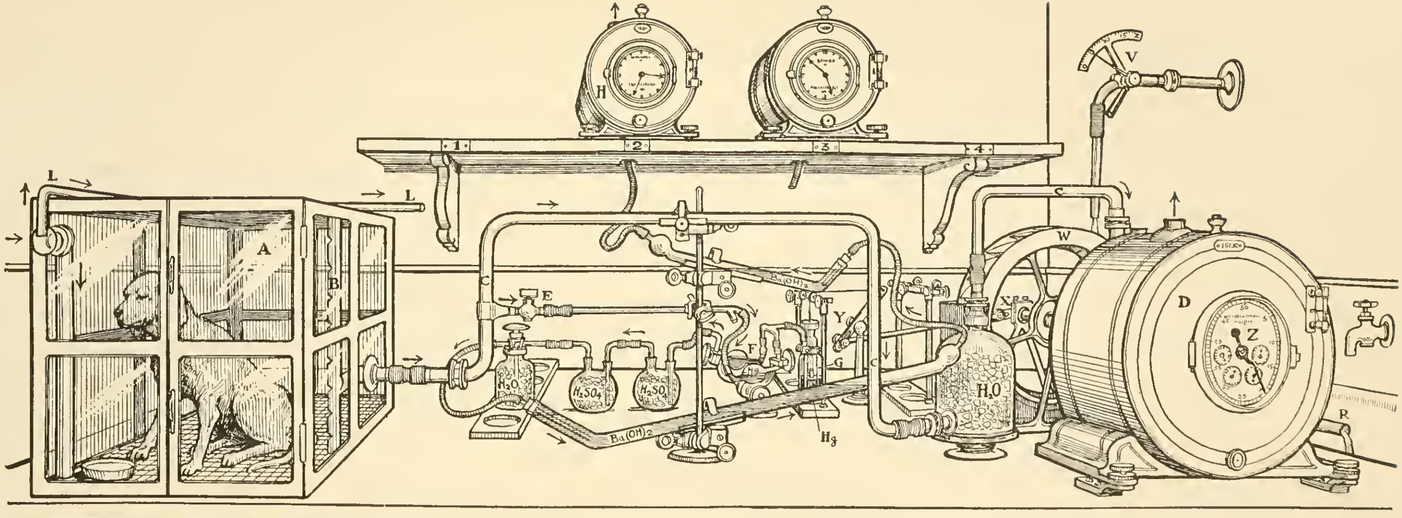

The smaller respiration apparatus of Pettenkoffer and Voit. Air enters the cage, A, at the upper left-hand corner. It is drawn out through openings in the tube B (so spaced as to insure thorough diffusion) through the tube, C, and the large H_2O flask, where it is saturated with moisture, to the gas meter, D, where it is measured. The meter is driven by a water wheel, W, rotated at a uniform rate of speed by a constant head of water pressure, V. At E a side tube leads off from C conveying a sample of cage air for analysis. This air is drawn through a mercury valve, F, by means of the mercury pump, G. The latter is operated by the mechanism, X, Y, connected with the water wheel. From the valve F, this air passes through two H_2SO_4 flasks and is then saturated with moisture so as to prevent loss of water from the $Ba(OH)_2$ tubes. Of course, the air, as it leaves the $Ba(OH)_2$ tubes, is saturated with moisture, and is measured by the small gas meter, H, just as in the case of the large meter, while in this saturated condition. A duplicate sample is led off at the same time through another branch of the tube, E, and through another system of vessels to the gas meter at 3. Through the branches of the tube, L, duplicate samples of the air which enters the cage are drawn in the same manner to similar valves, and then through similar vessels and tubes to meters placed at 1 and 4. (Tigerstedt's "Human Physiology.")

THE ELEMENTS

OF THE

SCIENCE of NUTRITION

BY

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To the Memory of
CARL VON VOIT
MASTER AND FRIEND
FROM WHOM THE AUTHOR RECEIVED THE INSPIRATION
OF HIS LIFE'S WORK
THIS VOLUME IS DEDICATED

"The greatest joy of those who are steeped in work and who have succeeded in finding new truths and in understanding the relations of things to each other, lies in work itself."

Carl von Voit.

PREFACE TO THE THIRD EDITION

In the preparation of the first edition of this book a decade ago the endeavor was made to admit to the introductory chapter only such material as appeared to be susceptible of scientific proof and to make it the key to the rest of the book. In this, the third edition, that chapter remains virtually unchanged. The rest of the book shows many important additions to the facts of metabolism and revisions of its theories.

The aim of the book remains the same, to review the scientific substratum upon which rests present-day knowledge of nutrition both in health and in disease. Throughout, no statement has been made without endeavoring to examine the evidence on which it is based.

Laboratory methods to explain the inner processes in disease have been applied to hospital patients for thirty years or more in Germany. In the United States great advances have lately been accomplished in this direction. If such investigations are still further promoted by their discussion here, this writing will not have been in vain.

The author would apologize to all whose claims of priority of discovery have not been duly recognized.

He gratefully acknowledges the helpful criticism of all those who have been his fellow-workers in the laboratory, especially John R. Murlin, E. F. Du Bois, and A. I. Ringer, who for periods of several years have been closely associated with him. He would also express his appreciation of the generous support of the experimental work in his laboratory by the authorities of the Cornell Medical College, as well as by Mrs. Russell Sage and the Trustees of the Russell Sage Institute of Pathology.

It is, furthermore, a privilege to recognize the great influence which a personal acquaintance with such men as F. G. Benedict and S. R. Benedict, Cathcart, Chittenden, Cremer, Dakin, Folin, Halliburton, Hopkins, Kossel, Levene, Magnus-Levy, Lafayette Mendel, Friedrich von Müller, von Noorden, Rubner, E. Voit, and Zuntz has had upon the conceptions of the subject of nutrition as set down in this book.

He wishes to express his great obligation to a former pupil, Dr. Margaret B. Wilson, who has painstakingly corrected and improved the manuscript and proof.

He is indebted to Dr. F. C. Gephart for the preparation of the index.

Finally, the writer desires to state that he has no intention of again revising this book. In another decade the development of scientific knowledge will probably permit the formulation of the subject from the standpoint of physical chemistry. It cannot now be so treated. The field is open. That the joy of the labor may be as great to him who next reviews the subject as it has been to the writer, is the earnest wish of

GRAHAM LUSK.

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NEW YORK CITY.
June, 1917.

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THE ELEMENTS OF THE SCIENCE OF NUTRITION

CHAPTER I

INTRODUCTORY

The earliest scientific observations concerning nutrition were founded upon the commonly noted fact that in spite of the ingestion of large quantities of food, a normal man did not vary greatly in size from year to year. It was understood early in the history of physiology that the weight added by the ingestion of food and drink was lost in the urine, the feces, and the "insensible perspiration." The "insensible perspiration" was partly in evidence when moisture of the warm breath condensed upon a cold plate. By it were meant the usually invisible exhalations from the body, which are now known to be carbon dioxid and water.

Sanctorius[1] made many experiments upon himself and others to determine the amount of insensible perspiration. An old cut shows him sitting in a chair suspended from a large steelyard. As a matter of routine he determined his own weight previous to each meal and then weighted the steelyard so as to counterbalance the additional food he proposed to eat. During the meal when the chair dipped he ended his repast.

In Section I, Aphorism II, Sanctorius gives the following curious advice: "If a physician who has the care of another's health is acquainted only with the sensible supplies and evacuations, and knows nothing of the waste that is daily made by

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[1] Sanctorius: "De medicina statica aphorismi," Venice, 1614. Translation by John Quincy, M.D., London, 1737.

the insensible perspiration, he will only deceive his patient and never cure him." Aphorism III reads: "He only who knows how much and when the body does more or less insensibly perspire will be able to discern when or what is to be added or taken away either for the recovery or preservation of health."

In 1668 John Mayow, writing in London, stated that the atmosphere contained a constituent which supported combustion as well as animal life.

The modern era of the science of nutrition was opened by Lavoisier in 1780. He was the first to apply the balance and the thermometer to the investigation of the phenomena of life, and he declared "La vie est une fonction chimique." The work of today is but the continuation of that done a century and more ago. Lavoisier and Laplace made experiments on animal heat and respiration. The great German chemist Liebig received his early training in Paris, residing there in 1822. Liebig's conception of the processes of nutrition fired the genius of Voit to the painstaking researches which laid the foundation of his Munich school. These have been repeated and extended by his pupils, of whom Rubner is chief, and by others the world over. Thus the knowledge often transmitted personally from the master to the pupil, to be in turn elaborated, had its seed in the intellect of Lavoisier. It was he who first discovered the true importance of oxygen gas, to which he gave its present name. He declared that life processes were those of oxidation, with the resulting elimination of heat. He believed that oxygen was the cause of the decomposition of a fluid brought to the lungs, and that hydrogen and carbon were produced in this fluid and then united with oxygen to form water and carbon dioxid. He said that perspiration regulated the quantity of heat lost from the body and that digestion replenished the blood with the materials eliminated through respiration and perspiration. It was he who first made respiration experiments on man, the results of which are briefly described in a letter to Monsieur

Terray,[1] written in Paris and dated November 19, 1790. There is no existing record of the apparatus with which Lavoisier worked and early obtained the following results. The more important conclusions Lavoisier sums up as follows:

1. The quantity of oxygen absorbed by a resting man at a temperature of 26° C. is 1200 *pouces de France*[2] hourly.
2. The quantity of oxygen required at a temperature of 12° C. rises to 1400 *pouces*.
3. During the digestion of food the quantity of oxygen amounts to from 1800 to 1900 *pouces*.
4. During exercise 4000 *pouces* and over may be the quantity of oxygen absorbed.

These remarkable results are in strict accord with the knowledge of our own day. We know more details, but the fundamental fact that the quantity of oxygen absorbed and of carbon dioxid excreted depends primarily on (1) food, (2) work, and (3) temperature was established by Lavoisier within a few years after his discovery that oxygen supported combustion. Writing in 1849 Regnault and Reiset say, "Les recherches modernes ont confirmé ces vues profondes de l'illustre savant."

It was, however, quickly noted that if carbon and hydrogen burned in the lungs, the greatest heat would be developed there, a result not in accordance with observation. It was then suggested that the blood dissolved oxygen, and that the production of carbon dioxid and water took place through oxidation within the blood. In 1837 Magnus discovered that the blood did hold large quantities of oxygen and carbon dioxid, which gave apparent support to this theory. Ludwig in his later years believed that the oxidation took place in the blood.[3] Through the critical studies of Liebig, which were published in 1842, it was seen that it was not carbon and

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[1] Report of the British Association for the Advancement of Science, Edinburgh, 1871, p. 189.

[2] 1 cubic pouce = 0.0198 liter.

[3] Oral statement to the writer.

hydrogen which burned in the body, but protein, carbohydrates, and fat. Liebig's original theory was that while oxygen caused the combustion of fat and carbohydrates, the breaking down of protein was caused by muscle work. It will be shown later that oxygen is not the cause of the decomposition of materials in the body, but that this decomposition proceeds from unknown causes, and the products involved unite with oxygen. The sum of these chemical changes of materials under the influence of living cells is known as *metabolism.* This process may involve two factors, *catabolism*, or the reduction of higher chemical compounds into lower, and *anabolism*, or the construction of higher substances from lower ones.

Liebig was also the father of the modern methods of organic analysis, and with him began the great accumulation of knowledge concerning the chemistry of the carbon compounds, including many products of the animal economy. These discoveries gave the world a knowledge of the constitution of foods, of urine, of feces, and of tissues, which was not possessed by Lavoisier.

Liebig applied to the problems of biology the mental wealth of the newer chemistry which he himself was creating. He knew that protein contained nitrogen, and in 1842 he suggested that the nitrogen in the urine might be made a measure of the protein destruction in the body.[1] Bidder and Schmidt[2] were the first to make systematic experiments upon this subject. They gave meat to dogs and cats and found that almost all the nitrogen contained in the meat was eliminated in the urine and in the feces. They[3] make the following striking statement, which rings quite true to modern thought concerning protein metabolism: "Almost all the nitrogen of protein and collagen is split from its combination and carries

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[1] Liebig: "Die organische Chemie in ihrer Anwendung auf Physiologie und Pathologie," 1842.

[2] Bidder and Schmidt: "Die Verdauungssäfte und der Stoffwechsel," 1852, pp. 333, 339.

[3] Bidder and Schmidt: *Ibid.*, p. 387.

with it enough carbon, hydrogen, and oxygen to form urea; the remaining part, containing five-sixths of the total heat value of the protein, undergoes oxidation to carbon dioxid and water which are eliminated in the respiration, the calorifacient function having been fulfilled." The results obtained by Bidder and Schmidt were attacked and were not finally established until proof was afforded by Carl v. Voit,[1] who established the fact that an animal could be brought into what he called nitrogenous equilibrium. In this condition the nitrogen of the protein eaten was equal to the nitrogen eliminated from the body in the urine and feces. Thus Voit[2] fed a dog for fifty-eight days with 29 kilograms of meat containing 986 grams of nitrogen, and found 982.8 grams of nitrogen in the excreta of the period. The amount of N in the urine was 943.7 grams, and in the feces 39.1 grams. The difference between the amount of nitrogen ingested and that recovered in the excreta was only $\frac{3}{10}$ of 1 per cent. It therefore seemed extremely probable that the excretory outlet for protein nitrogen was in the urine and in the feces and that other sources of its loss were normally negligible. But in order to establish the fact it was necessary to consider the following questions:

Is the nitrogen of the air built up into organic compounds within the body? Is any protein nitrogen given off as nitrogen gas? As ammonia gas? In the sweat? How much is lost through the growth of the hair, nails, and epidermis?

Lavoisier had said that nitrogen gas had nothing to do with respiration. Regnault and Reiset[3] sometimes found that animals under a bell-jar absorbed nitrogen gas and at other times gave it off. The quantity in both cases was extremely small and can be explained by slight errors in gas analysis due to inexact temperature records. Regnault and Reiset found no measurable quantities of ammonia or of

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[1] Voit: "Physiol. Chem. Untersuchungen," 1857.

[2] Voit: "Zeitschrift fur Biologie," 1866, ii, 35.

[3] Regnault and Reiset: "An. de chimie et phys.," Paris, 1849, Sec. 3, Tome xxvi.

sulphur-containing gases in the expired air, and they discovered that hydrogen might replace nitrogen in the atmosphere without affecting the course of metabolism.

The experiments of Bachl[1] showed that a rabbit with a tracheal cannula could be made to expire for six hours through Nessler's reagent without the indication of a trace of ammonia in the breath. This has also been shown after making an Eck fistula in a dog,[2] where there is an increase in the amount of ammonia in the blood and in the urine. The lungs are not permeable to ammonia.[3] The ordinary insensible perspiration is not accompanied by any appreciable loss of nitrogenous excreta, although profuse sweating certainly brings out some urea, uric acid, and other nitrogen extractives normally excreted in the urine. The experiments of Benedict[4] show that the cutaneous excretions of a resting man may amount to 0.071 gram nitrogen *per day;* of a man at moderate work to 0.13 gram *per hour*, and at hard work for four hours to 0.22 gram *per hour.*

Voit[5] collected the hair and epidermis from a dog for 565 days and found an average daily output of 1.2 grams with 0.18 gram of nitrogen. Moleschott[6] cut the hair and nails of several men once a month. The daily outgrowth of hair was 0.20 gram with 0.029 gram of nitrogen, and of nail substance 0.005 gram with 0.0007 gram of nitrogen. The waste through the human epidermis has not been measured, but it must be very slight. The above sources of error were thus shown to be negligible.

The view that the nitrogen of the urine and feces could be made a measure for the determination of protein metabolism was thus securely established. Urea, the principal nitrogenous end-product derived from protein, was therefore shown to be not an adventitious product, but one normally pro-

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[1] Bachl: "Zeitschrift für Biologie," 1869, v, 61.
[2] Salaskin: "Zeitschrift für physiologische Chemie," 1898, xxv, 463.
[3] Magnus: "Archiv für ex. Pathologie und Pharmakologie," 1902, xlviii, 100.
[4] Benedict: "Journal of Biological Chemistry," 1906, i, 263.
[5] Voit: "Zeitschrift für Biologie," 1866, ii, 207.
[6] Moleschott: "Untersuchungen zur Naturlehre," xii, 187.

portional to the protein destruction. It was known that meat protein in general contained about 16 per cent. of nitrogen, or 1 gram of nitrogen in 6.25 grams of protein. Therefore for every gram of nitrogen found in the excreta, 6.25 grams of protein have been destroyed in the body. It is evident that if protein nitrogen be retained in the body a new construction of body tissue is indicated, whereas if more nitrogen is eliminated than is ingested with the food, a waste of body tissue must take place. The discovery of the method of calculating the protein metabolism led Voit to suggest to Pettenkofer that he construct an apparatus with which the total carbon excretion might be measured, including that of the respiration as well as that of the urine and the feces. Voit saw that with these data it would be possible to determine just how much of each food-stuff was actually burned in the human body. He has described the delight which he and Pettenkofer experienced when their wonderful machine began to tell its tale of the life processes. The cost of the apparatus, which was considerable, was defrayed by King Maximilian II of Bavaria.

It has been stated that the form of Lavoisier's respiration apparatus is unknown. In 1850 Regnault and Reiset[1] published an account of respiration experiments in which small animals were placed under a bell-jar containing a known quantity of oxygen. The air was kept free from carbon dioxid by pumping it through potassium hydrate, and oxygen was added from time to time. The gaseous exchange between the animal and its environment could be readily ascertained by determining the amount of carbon dioxid given off and the amount of oxygen absorbed. No attempt was made to determine from what materials the carbonic acid arose. The method of Regnault and Reiset placed the animals in a confined space where poisonous exhalations other than carbon dioxid could collect, and where the atmosphere became saturated with water. However, these factors were without

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[1] Regnault and Reiset: "An. d. Chem. und Pharm.," 1850, lxxiii, 92, 129, 257.

influence on the health of their animals. They planned to work in one of the large hospitals in Paris, but, unfortunately, the project proved too costly and had to be renounced. They write, "L'étude de la respiration de l'homme dans ses divers états pathologiques nous paraît un des sujets les plus dignes d'occuper les hommes qui se vouent à l'art de guérir: elle peut donner un diagnostic précieux pour un grand nombre de maladies et rendre plus évidentes les revolutions qui surviennent dans l'économie." Although Regnault and Reiset had no definite idea of the materials which were oxidized in the animals with which they were experimenting, we find that Bischoff and Voit[1] tried to read such interpretations into the work of Regnault and Reiset. Thus Bischoff and Voit determined the quantity of nitrogen in the urine of a starving dog, which indicated that he had burned in twenty-four hours 218 grams of his own "flesh." The flesh was calculated from the nitrogen elimination on the basis of the knowledge that fresh meat contains 3.4 per cent. of nitrogen. Many of the older experiments were computed on this basis. It was shown that the 218 grams of "flesh" contained 40 grams of carbon. Bischoff and Voit estimate from the experiments of Regnault and Reiset that a meat-fed dog of a weight similar to the above would give off 250 grams of carbon and absorb 900 grams of oxygen in the respiration of twenty-four hours. These figures indicated to Bischoff and Voit that the extra carbon elimination was due to the combustion of fat, and they reached the conclusion that the waste of the body in starvation is dependent on the metabolism of protein and fat. Correct results, however, were attainable only by combining the two methods, so that both the quantity of the nitrogen and carbon of the urine and feces and the amount of carbon dioxid of the respiration during the same period of time could be ascertained. This was accomplished by the respiration apparatus of Pettenkofer.

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[1] Bischoff and Voit: "Die Gesetze der Ernährung des Fleischfressers," 1860, p. 43.

The problem to be solved by Pettenkofer included the maintenance of a man in normal surroundings. A small room was therefore constructed which was well ventilated by a current of air. This air entered the chamber freely through an opening in connection with a large room outside and was aspirated from a second opening in the chamber, through a large gas-meter, where its volume was measured (500,000 liters per day). It was evidently impracticable to determine all the carbon dioxid in this large volume of air, but its amount was calculated from the analysis of duplicate samples continually withdrawn from the air leaving the chamber during the time of the experiment. Each sample, as it was pumped out, was made to pass over calcined pumice stone soaked in sulphuric acid, to remove the water. Next it bubbled through baryta water to remove the carbon dioxid, and then passed through a small gas-meter, where the volume of the sample was measured. After this fashion the amount of carbon dioxid and water coming from the air of the chamber was determined in duplicate. Other duplicate analyses of the air taken outside the ventilator just before it entered the chamber were simultaneously made in the same manner as were the analyses of the chamber air itself. Knowing the quantity of carbon dioxid and water entering and leaving the room, it was easy to calculate how much was derived from the man living in it during the period of experimentation. The experimenters failed to find any other gaseous exhalation from a man, such as ammonia, hydrogen, or methane, which could vitiate their results. Control experiments were made by burning a candle or evaporating a known weight of water within the room. Analysis showed that the carbon dioxid and water so produced were measurable within 1 per cent. of error.

As an illustration of the practical working of the respiration apparatus the first experiment of Pettenkofer and Voit,[1] which gives the metabolism in a starving man, will be described.

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[1] Pettenkofer and Voit: "Zeitschrift für Biologie," 1866, ii, 478.

The man was allowed a small quantity of Liebig's extract of beef, as the experimenters did not at that time realize the very slight discomfort usually entailed by total abstinence from food. As Liebig's extract has no nutritive value, its effect has been counted out in the following description.

The subject, on entering the living-room of the apparatus, weighed 71.090 kilograms, and he drank during the day 1.0548 liters of water, making a total body weight of 72.1448 kilograms. Twenty-four hours later he weighed 70.160 kilograms and his excreta had amounted to 0.7383 kilogram carbon dioxid, 0.8289 kilogram water from lungs and skin, and 1.1975 kilograms of urine. The final body weight plus all the excreta amounted to 72.9247 kilograms. A total body weight of 72.1448 kilograms was converted into a body weight plus excreta amounting to 72.9247 kilograms. The difference is due to oxygen absorbed. The difference of 0.7799 kilogram represents the amount of oxygen needed to convert the body substance lost into the excretory products obtained. The tabular statement reads:

MAN—STARVATION

	Kg.		Kg.
Weight at start	71.090	Weight at end	70.160
Water drunk	1.0548	Carbon dioxid	0.7383
		Water in respiration	0.8289
Oxygen absorbed	0.7799	Urine	1.1975
	72.9247		72.9247

The analysis of the urine showed 12.51 grams of nitrogen and 8.25 grams of carbon. A calculation gives the amount of carbon in the respiration as 201.3 grams. If we neglect the feces as being too small in starvation to influence the results, we find that the total carbon elimination for twenty-four hours was 209.55 grams, and the total nitrogen 12.51. In the Liebig extract ingested there were 2.44 grams of carbon and 1.18 grams of nitrogen, which must be deducted from the above in order to obtain the strict loss of carbon and nitrogen from the body during the period of starvation. These values are:

C	207.11 grams.
N	11.33 "

These two figures enabled Pettenkofer and Voit to calculate what substances had burned in the body. As every gram of nitrogen in the excreta is approximately represented by the destruction of 6.25 grams of meat protein, the amount of such protein destroyed by the man was 70.81 grams. It has been found that for every gram of nitrogen present in meat protein there are 3.28 grams of carbon. It is therefore easy to estimate that destruction of protein represented by 11.33 grams of nitrogen involved the elimination of 37.16 grams of carbon. Now, the man eliminated 207.11 grams of total carbon, from which this protein carbon may be deducted, leaving as residue 169.95 grams, which must have originated from a source other than protein. The possible sources are two in number—carbohydrates and fats. In starvation no carbohydrates are ingested and their supply in the form of reserve glycogen is usually counted as being negligible in such experiments as these. The only other source from which the 169.95 grams of extra carbon could have been derived is fat, and as fat contains 76.52 per cent. of carbon, a destruction of 222.1 grams of fat may be calculated. This fasting man therefore destroyed:

Protein	70.81 grams.
Fat	222.1 "

That such metabolism actually did take place was further indicated by the comparison of the amount of oxygen needed for the destruction of the above constituents, and the amount of oxygen absorption as determined by the experiment.

From the constituents of the protein and fat destroyed, Pettenkofer and Voit deducted the constituents of the urine, which contains part of the C and H belonging to protein. The balance of the carbon and hydrogen was fit for oxidation to carbon dioxid and water. Their calculation may thus be presented:

	Weight in Grams.		
	C	H	O
Composition of the protein burned	37.16	5.8	17.1
Composition of fat burned	169.95	25.7	25.1
Total C, H, and O metabolized	207.11	31.5	42.2
Deduct quantity in the urine	8.2	2.0	7.6
Balance available for respiratory CO_2 and H_2O	198.9	29.5	34.6
Oxygen required	530.4	235.7	
Total O required for the formation of CO_2 and H_2O			766.1
Less O in the protein and fat			34.6
Oxygen actually required			731.5
Oxygen absorption as determined			779.9
Difference			48.4

We may reach the same result by using the most modern figures for the oxygen requirement in the metabolism of the food-stuffs. We now know that to burn 100 grams of meat protein requires 133.43 grams of oxygen, and to burn 100 grams of fat requires 288.5 grams, and to burn 100 grams of starch 118.5 grams. This being true, there are required:

	Oxygen.
For 70.81 grams protein	94.44 gm.
For 222.1 grams fat	639.55 gm.
Total required	733.99 gm.
Oxygen absorption as found	779.9 gm.
Difference	45.91 gm.

Had carbohydrates burned, less oxygen would have been needed, since carbohydrates contain a larger proportion of oxygen than fats. Had the extra 169.95 grams of carbon been due to the combustion of starch (or glycogen), 382 grams would have burned, requiring 452.7 grams of oxygen instead of 639.5 grams for fat. Pettenkofer and Voit found in the amount of oxygen absorption a confirmation of their belief that the fasting organism supports itself by the combustion of its own protein and fat.

It is apparent from this discussion that *the quantity of oxygen needed in metabolism depends upon the chemical composition of the* *material that burns in the organism*, and also that the relation between the amount of oxygen absorbed and carbon dioxid excreted depends on the same factor. Regnault and Reiset frequently observed that this latter relationship was variable. The ratio of the *volume* of carbon dioxid expired to the *volume* of oxygen inspired during the same time is called the *respiratory quotient* (see p. 57). When carbohydrates burn, the R. Q. is unity; that is, for every hundred volumes of carbon dioxid excreted a hundred volumes of oxygen are absorbed. When protein burns the quotient is $\frac{\text{Vol. CO}_2}{\text{Vol. O}_2} = \frac{78.1}{100}$ or 0.781, and when fat burns the quotient is 0.71. Pettenkofer and Voit calculated that the respiratory quotient in their fasting man was 0.69. This indicated a combustion of fat in the organism.

The further researches of Pettenkofer and Voit were founded on the principles described in the above experiment on a fasting man. If meat and fat were ingested, the carbon and nitrogen excreta were collected, and from these data it was determined how much of each food-stuff was oxidized and whether there was a storage of either in the body or a loss of either from the body. If a mixed diet which included carbohydrates were given, the carbon dioxid elimination increased and the oxygen absorption was such as indicated the combustion of carbohydrates. It was assumed that after deducting the protein carbon from the total carbon eliminated, the balance of extra carbon was derived from the destruction of the carbohydrates in so far as these were ingested; any carbon in excess of this was attributed to fat combustion.

Voit,[1] in his necrology of Pettenkofer, writes: "Imagine our sensations as the picture of the remarkable processes of the metabolism unrolled before our eyes, and a mass of new facts became known to us! We found that in starvation protein and fat alone were burned, that during work more fat was burned, and that less fat was consumed during rest, especially during sleep; that the carnivorous dog could maintain himself on an exclusive protein diet, and if to such a protein diet fat

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[1] Voit: "Zeitschrift für Biologie," 1901, xli, 1.

were added, the fat was almost entirely deposited in the body; that carbohydrates, on the contrary, were burned no matter how much was given, and that they, like the fat of the food, protected the body from fat loss, although more carbohydrates than fat had to be given to effect this purpose; that the metabolism in the body was not proportional to the combustibility of the substances outside the body, but that protein, which burns with difficulty outside, metabolizes with the greatest ease, then carbohydrates, while fat, which readily burns outside, is the most difficultly combustible in the organism."

Since the days of these researches repeated experiments have established the verity of the conclusions drawn. It is interesting to note that among the earliest experiments made were some upon patients in pathologic conditions, one suffering from leukemia, another from diabetes.

Besides the influence of foods upon metabolism, the changes brought about by exercise, temperature, and drugs were investigated not only by the Munich school, but by many other workers. Similar investigations are actively progressing today.

Among the important conclusions reached by Voit was that concerning the manner of the metabolism. It has been stated that Liebig believed that fat and carbohydrates were destroyed by oxygen, while protein metabolism took place on account of muscle work.

Voit[1] *showed that muscle work did not increase protein metabolism and that the metabolism was not proportional to the oxygen supply.* The oxygen absorption apparently depended upon what metabolized in the cells. Voit believed that the cause of metabolism was unknown, that the process was one of cleavage of the food molecules into simpler products, which could then unite with oxygen. Yeast cells, for example, convert sugar into carbonic acid and alcohol without the intervention of oxygen. In like manner the first products of the decomposition of fat, sugar, and protein are formed in

[1] Voit: "Zeitschrift für Biologie," 1866, ii, 535.

metabolism through unknown causes. Some of these preliminary decomposition substances may unite with oxygen to form carbon dioxid and water, others may be converted into urea, while others under given circumstances may be synthesized to higher compounds. In any case *the absorption of oxygen does not cause metabolism, but rather the amount of the metabolism determines the amount of oxygen to be absorbed* (see p. 32).

The statement is frequently met with in the literature of the subject that such and such a disease is the consequence of deficient oxidative power in the tissues. For example, it has been stated that alcohol decreases the oxidative power of the liver for uric acid.[1] Such apparent decrease in oxidative power may, however, be due to the fact that the normal oxidizable cleavage products are not formed and, therefore, no oxidation can take place. It is not due to lack of oxygen that sugar is not oxidized in diabetes, or cystin in cystinuria. There is the normal supply of oxygen present, but the cleavage of these substances into bodies which can unite with oxygen cannot be effected, and hence they cannot be metabolized.

Voit's pupil, Lossen,[2] showed that the carbon dioxid elimination in respiration was independent of the ventilation of the lungs except in so far as forced breathing increased the muscular work and the consequent output of carbon dioxid.

When the depth of respiration was voluntary the results were as follows:

Number of Respirations per Minute.	Volume of Expired Air in 15 Minutes.	Volume of One Respiration.	CO_2 in 15 Minutes.
	Liters.	C.C.	Grams.
5	75.1	1002	7.96
10	83.6	558	7.44
15	94.4	420	7.32
20	120.3	401	8.14
30	121.0	269	7.18
40	138.5	231	6.76
60	182.7	203	6.63

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[1] Beebe, S. P.: "American Journal of Physiology," 1904, xii, 36.

[2] Lossen: "Zeitschrift für Biologie," 1866, ii, 244; 1870, vi, 298.

Pflüger,[1] who through different reasoning came to the same conclusion as Voit, devised an experiment in which a rabbit breathed quietly through a cannula, and the oxygen absorption was compared with that of the same animal when rapid artificial ventilation of the lungs with air took place, producing apnea or hyperarterialization of the blood. There was no difference, as is seen from the following table:

	Oxygen Absorbed in C.C. During 15 Minutes.	
	Normal respiration.	Apnea.
Series I	201.66	203.88
Series II	203.21	210.47

From these experiments it is made sure that the respiration does not cause or regulate metabolism. On the contrary, the metabolism regulates the respiration. *The metabolism of the tissues, through its oxygen requirement and its carbon dioxid production, changes the condition of the blood and thereby regulates the respiration. These distinctions are of fundamental importance.*

Thus far the history of the principles which underlie the exact measurement of the metabolism has been briefly given. By metabolism is meant the chemical changes of materials under the influence of living cells. The first cause of these chemical changes, it has been seen, is unknown, but their results lead to motions of the smallest component parts of protoplasm, motions whose totality we call life. Phenomena of life are phenomena of motion due to liberation of energy in the breaking down of molecules. The motions are principally manifested as heat, mechanical energy, and electric currents. In the organism mechanical energy may be converted into heat, as appears when work of the heart is converted into heat by the friction of the blood upon the capillaries. Also the current of electricity developed at each systole of the heart, or in any other active tissue, is resolved into heat. Thus heat

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[1] Pflüger: "Archiv für die ges. Physiologie," 1877, xiv, 1.

may become a measure of the total activity of the body. It is derived from the total metabolism and must be dependent on it and be a measure of it. Hence the physical activities noted in life are the results of chemical decompositions. Metabolism vivifies the energy potential in chemical compounds.

Lavoisier[1] was the first to recognize that animal heat was derived from the oxidation of the body's substance and to compare animal heat to that produced by a candle. To prove this he burned a known quantity of carbon in an ice-chamber and noted the amount of ice melted. He then calculated the amount of heat produced from a unit of carbon. He and Laplace put a guinea-pig in an ice-chamber and noted the amount of ice which melted during ten hours and calculated the heat given off from the animal. They then determined how much carbon dioxid the guinea-pig gave off. The animal yielded 31.82 calories to the ice-chamber, while a calculation from the respiratory analysis showed that 25.408 calories could have been derived by the burning of enough carbon to yield the same amount of carbon dioxid as was eliminated by the animal.

Lavoisier realized several of the errors in his work. For example, the calorimetric determination on the animal was made at a different temperature from that of the respiratory experiment, and Lavoisier knew that cold would raise the carbon dioxid output. Also cold reduced the heat in the animal itself, and, further, the water of respiration was added to that of the melting ice. But Lavoisier concluded that the source of the heat lay in the oxidation of the body.

Crawford, in England in 1777, found after burning wax and carbon, or on leaving a live guinea-pig in his water calorimeter, that for every 100 ounces of oxygen used the water was raised the following number of degrees Fahrenheit:

Wax	2.1
Carbon	1.93
Guinea-pig	1.73

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[1] Lavoisier and Laplace: Académie des Sciences, 1780, p. 379.

Crawford concluded that the heat above produced was due to the transformation of pure air into fixed air (carbon dioxid) and water.

The methods of Crawford, though primitive, were based on fundamental principles, for according to the modern computation of Zuntz the values of heat production where 1 liter of oxygen is used to burn the different food-stuffs in the body are very nearly identical (see p. 62).

In 1823 the French Academy awarded a prize for the best essay on the subject of animal heat. Depretz and Dulong competed for the prize and it was awarded to the former.

Depretz[1] calculated the amount of heat which would have been liberated in burning the carbon and hydrogen of the metabolism to carbon dioxid and water, and compared this with the amount of heat given off by the animal. The heat as calculated was only 74 to 90 per cent. of what was found, a discrepancy due to faults in the method employed (see p. 43). So Depretz concluded that although the respiration was the principal source of animal heat, food, the motion of the blood, and friction yielded the remainder. Interpretation along the lines of the law of the conservation of energy was obviously beyond the ideas of the time.

Dulong's[2] experiments also led to the same conclusion, that oxidation was insufficient to explain the cause of animal heat, and that there must be other sources of it.

Regnault and Reiset, writing in 1849 regarding the computation of heat production from the oxygen absorbed by an animal, remark, "The phenomena are evidently so complex that it is scarcely probable that one will ever be able to submit them to calculation."

About 1842 James P. Joule supplied the chief experimental data which established the mechanical equivalent of heat. In 1845 J. R. Mayer laid down the law of the conservation

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[1] Depretz: "Journal de Physiologie," 1824, iv, 143.

[2] Dulong: *Ibid.*, 1823, iii, 45.

of energy, and in 1847 Helmholtz independently made the same discovery. Both contributions were rejected by the leading German scientific journal of the day.[1] This should encourage all workers to rest assured of the ultimate recognition of work that is worth while.

Energy cannot arise from nothing, nor can energy disappear into nothing. Where energy is active it must have been elsewhere potential. The sum total of energy remains constant in the universe, but energy may vary in kind. The kinds include mechanical energy, heat, electricity, magnetism, and potential energy. The source of energy on the earth is the sun, excepting the energy of the tides, which is due principally to the moon. The sun unevenly warms the atmosphere, producing winds which drive ships and windmills. The sun's heat lifts the vapor of water into the atmosphere, producing rain, in consequence of which rivers are made to turn machinery. The sunlight acts upon a mixture of hydrogen and chlorin gas, causing them to unite with a loud explosion, and the sun acts upon the green leaf of the plant, causing it to unite carbon dioxid and water, with the production of formic aldehyd, which is built up into sugar, oxygen being given off in the process. The sun's energy required to build up the compound becomes latent or potential in it. Whenever and wherever this sugar is again converted into carbon dioxid and water by oxidation, exactly the same quantity of energy taken from the sun and made potential in the sugar is set free. This sugar in the plant may be further converted into starch, cellulose, fat, and possibly into protein. Plants furnish wood and coal as fuel for the steam-engine. They also furnish the basis of animal food, yielding substances which can build up animal tissues, and which can furnish the energy necessary to maintain those motions in the cells whose aggregate is called life. These motions appear in the body as heat, mechanical work, and electric currents, all of which may be measured as heat. Is this energy completely derived from

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[1] "Wiener klin. Wochenschr.," S. Exner, 1914, xxvii, 1529.

the metabolism? This question is but the continuation of the old one of Lavoisier in the light of newer science.

Bischoff and Voit[1] in 1860 still calculated the heat value of the metabolism from the heat developed in burning the carbon and hydrogen elements of the metabolism. They recognized, as had Bidder and Schmidt[2] before them, that this was a false method, and stated that they should employ the calorific value of fat, starch, and protein, less the urea, since they recognized that urea was capable of undergoing combustion with liberation of heat.

In 1860 Voit[3] took a Thomson calorimeter with him from London to Munich. After Frankland's determination of the heat value of the various food-stuffs and urea Voit[4] prepared a table in 1866 for use in his lectures showing that the metabolism of the fasting man experimented on by Pettenkofer and Voit indicated the production of 2.25 million small calories, while the metabolism on a medium diet was 2.40 million calories.

In 1873 Pettenkofer and Voit[5] calculated that 100 grams of fat were the physiologic equivalent of 175 grams of starch. Liebig at that time had suggested that the amount of these substances which could be burned by a man was proportional to the oxygen supply.

Voit, not content with his results, suggested to Schürmann in 1878–79 that he carry on experiments to see in what way carbohydrates and fat were interchangeable in nutrition. Schürmann died before the work was completed and the investigation was continued by Rubner. *The isodynamic law, which showed that the food-stuffs may under given conditions replace each other in accordance with their heat-producing value, was the result.*

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[1] Bischoff and Voit: "Die Gesetze der Ernährung des Fleischfressers," 1860, p. 43.

[2] Bidder and Schmidt: "Verdauungssäfte und Stoffwechsel," 1852, p. 353.

[3] Voit: "Münchener medizinische Wochenschrift," 1902, xlix, 233.

[4] Voit: *Ibid.*

[5] Pettenkofer and Voit: "Zeitschrift für Biologie," 1873, ix, 534.

Rubner gives the following as the quantities of the different food-stuffs which are *isodynamic:*

100 gm. fat.
232 gm. starch.
234 gm. cane-sugar.
243 gm. dried meat.

After Stohmann[1] published his research on the calorific value of foods, urea, etc., Voit commenced the construction of a calorimeter for the measurement of the heat eliminated from the body of a man whose metabolism was simultaneously determined. The results obtained by the use of this machine were never published.

Rubner[2] in Voit's laboratory during this same period was making a series of valuable calorimetric determinations. The heat value to the body of burning starch and fat were obviously the same as that determined in the calorimeter, since in both cases the same end-products, carbon dioxid and water, resulted. The heat value of protein in the calorimeter was different from its fuel value to the body, since the end-products were different in the two cases. When protein is oxidized in the body the products of its metabolism are lost in three different ways—through the respiration, urine, and feces. The two last contain latent heat lost to the body, which must be deducted from the heat value of protein determined calorimetrically.

The custom of Stohmann and previous authorities had been to deduct the heat value of urea from the heat value of protein in order to obtain the actual physiologic or fuel value of protein for the organism. But in the earliest experiments of Pettenkofer and Voit[3] it was recognized that in starvation and after the ingestion of meat there was a much larger output of carbon in the urine than corresponded to the quantity of urea present. The ratio of nitrogen to carbon was nearly constant in the urine when the conditions of feeding

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[1] Stohmann: "Journal für praktische Chemie," 1885, xxxi, 273, and earlier papers.

[2] Rubner: "Zeitschrift für Biologie," 1885, xxi, 250, 337.

[3] Pettenkofer and Voit: *Ibid.*, 1866, ii, 471.

were similar. If urea alone were present, Rubner estimated there would be 0.429 gram of C to 1 of N or an N : C = 1 : 0.429. In starvation the urine contains extractive nitrogen (creatinin, uric acid, etc., having relatively more carbon than urea) which has been derived from the breaking down of tissue protein, and the ratio is N : C = 1 : 0.728. When meat was ingested the fact that the food contained these extractives made the C : N ratio 0.610. And even after six days' ingestion of meat washed free from extractives the urine of the seventh and eighth days still showed an elimination of carbon other than that due to urea, as was indicated by the ratio 0.532. Therefore, from the metabolism following the ingestion of the proteins of washed meat small amounts of carbon compounds other than urea are eliminated in the urine.

Rubner saw that it was the heat value of the urinary constituents themselves which had to be subtracted from the heat value of protein if the fuel value of protein to the body was to be determined.

The following table shows Rubner's results after burning the dry urine:

CALORIFIC VALUE OF URINE

Material Burned.	C : N.	Calories from 1 Gram.	Calorific Value of 1 Gram N.
Urea	0.429	2.523	5.41
Urine after feeding protein	0.532	2.706	5.69
Urine after feeding meat	0.610	2.954	7.46
Urine in starvation	0.728	3.101	8.49

Benedict and Milner[1] report that the average C : N ratio in man when he partakes of a mixed diet is 0.75 and the calorific value of a gram of urinary nitrogen is 8.09. When a diet which is high in carbohydrate is ingested the value of a gram of urinary nitrogen may be from 11 to 13 calories,[2]

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[1] Benedict and Milner: United States Dept. of Agriculture, Office of Experiment Stations, 1907, Bulletin 175, p. 144.

[2] Tangl. "Archiv für Physiologie," 1899, Supplement Bd., p. 251.

an increase which is due to the appearance of products of the intermediary metabolism of glucose (see p. 208), although no glucose itself is present.[1]

It was not alone necessary to know the heat value of the urine excreted, but also that of the feces. Rubner found that after giving 100 parts of dry muscle containing 5.5 grams of ash there was an elimination of 38.2 grams of the organic part in the urine and 2.7 grams in the feces. The following table represents this division of material in the excreta:

	C.	H.	N.	O.
Composition of 100 parts dry muscle	50.5	7.6	15.4	20.97
Urine contains 38.2 parts	9.63	2.52	15.16	10.9
Feces contain 2.7 parts	1.67	0.25	0.24	0.54
Excreted in urine and feces	11.30	2.77	15.40	11.44
Balance for respiration	39.2	4.8		9.53

Rubner determined the amount of heat produced from 1 gram of ash-free feces after meat ingestion and found it to be 6.127 calories, while 1 gram of ash-free feces after protein (washed meat) ingestion yielded 6.852 calories. The total calorific value of 1 gram of beef muscle when Rubner burned it in the calorimeter was 5.345 calories. He had now the principal data required to determine its heat value in the body. If from 100 grams of meat 2.7 grams appear as feces having a calorific value of 6.127 calories per gram, then there is here a loss of 6.127 × 2.7 = 16.83 calories. If from every 100 grams of meat containing 15.4 grams of nitrogen 15.16 grams of the latter appear in the urine and such urine produced by ingesting meat has a calorific value of 7.46 calories for every gram of nitrogen present, then the energy loss in the urine would be 7.46 × 15.16 = 112.94 calories. For dry muscle substance we find therefore:

				Calories.
100 grams muscle				534.5
Waste	Urine	112.94	Total	129.77
	Feces	16.83		
Fuel value of 100 grams of dry muscle				404.73

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[1] Reale: "Biochemische Zeitschrift," 1913, lvii, 143.

From this value there must be a slight deduction for the heat present in the protein in its colloidal state but lost on drying, and for the heat of solution necessary to dissolve urea and other urinary constituents. Rubner estimates these as:

Heat for the imbibition of protein	2.688
Heat for solution of urea	1.989
	4.677

Subtracting 4.67 from 404.73 leaves 400.06 calories as the maximum of energy obtainable from 100 grams of the dried solids of meat. The calorimeter shows a heat value of 534.5 calories for the same protein. Of this, 400.06 calories, or 74.9 per cent., are available in the organism, while the remainder, or 25 per cent., goes to waste.

A further calculation shows that every gram of nitrogen in the urine and feces represents an elimination of heat from protein metabolism equal to 25.98 calories. The heat value of protein under the different physiologic conditions was estimated by Rubner after the above fashion, and may thus be tabulated:

CALORIFIC VALUE OF PROTEIN IN NUTRITION

	Calories Yielded by Metabolism of 100 Grams of Protein in the Body.	Heat Value in Calories of Protein Metabolism Yielding 1 Gm. of N. in the Excreta.
After protein (washed meat) ingestion	442.4	26.66
After meat ingestion	400.05	25.98
Starvation	384.2	24.98

If we know the amount of nitrogen in the excreta we can calculate from these standard figures of Rubner the heat value of the protein metabolism to the body. Rubner found that the heat value of 1 gram of pig's fat (lard) was 9.423 calories. Since fat contains 76.5 per cent. of carbon, it could be calculated that for every gram of carbon eliminated in the respiration, which was the result of fat metabolism, 12.3

calories must have been liberated in the body. These figures enabled Rubner to calculate the amount of heat liberated by the fasting man of Pettenkofer and Voit, whose metabolism we have already discussed. The N excreted was multiplied by 24.98 and the fat carbon by 12.3 which gave the total heat value of the period:

Heat from protein (11.33 Gm. N × 24.98)	283 Cal.
Heat from fat (169.95 C × 12.3)	2091 Cal.
Total heat value of the metabolism as calculated	2374 Cal.

Rubner applied such calculations as these to the material at hand in the literature of the time, and discovered that *the heat value of the metabolism of the resting individual is proportional to the area of the surface of his body.* For example, a man in starvation, or on a medium diet, an infant at the breast, and a starving dog were shown to give off similar quantities of heat per square meter of surface. To these Rubner subsequently added the results of his researches upon a dwarf. The following tables illustrate this point:

	YIELD OF CALORIES PER SQ. M. SURFACE IN 24 HOURS.
Adult man in starvation	1134
Dog in starvation	1112
Adult man on a medium mixed diet	1189
Breast-fed infant	1221
Dwarf (weight = 6.6 Kg.) medium mixed diet	1231

This law, that an animal in starvation or on a medium diet and at an environmental temperature of 18° gives off the same quantity of heat per square meter of surface, can be extended so that it applies to all warm-blooded animals. Thus E. Voit[1] has collected data for the following table:

	Weight in Kg.	CALORIES. Per Kilo.	CALORIES. Per Sq. M. Surface.
Pig	128.0	19.1	1078
Man	64.3	32.1	1042
Dog	15.2	51.5	1039
Goose	3.5	66.7	967
Fowl	2.0	71.0	947
Mouse	0.018	654.0	1188

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[1] E. Voit: "Zeitschrift für Biologie," 1901, xli, 120.

Recent work has confirmed the validity of this "law of surface area," but has somewhat modified the idea of the conditions under which it finds expression (see Chapter IV).

Rubner from his work on protein considered that the heat value of 1 gram in an average mixed diet might well be placed at 4.1 calories. Of course, such a mixed diet would contain casein (4.4 cal.), the organic substance of meat (4.233 cal.), and vegetable proteins (3.96 cal.). The daily food allowance for animal protein was put at 60 per cent., for vegetable protein at 40 per cent., of the total protein in the mixed dietary. For the value of neutral fats Stohmann's figures for olive oil, fat of animal tissue, and butter fat were averaged as follows:

Olive oil	9.384	Calories per Gm.
Animal tissue fat	9.372	" "
Butter fat	9.179	" "
Average	9.312	" "

For the heat value of 1 gram of fat in a mixed diet Rubner therefore adopted the value 9.3.

The following heat values have been found for carbohydrates:

	Stohmann.	Rubner.
Glucose	3.692	3.755
Lactose	3.877	
Sucrose	3.959	4.001
Starch	4.116	

The variations in heat value are principally due to variations in the water content of the different molecules. Considering the predominating importance of starch in the average diet, Rubner gave the value of 4.1 to the group of carbohydrates in the foods.

Rubner's "standard values" have been widely used throughout the world in determining the average fuel value of a mixed diet. They are:

1 gram of protein	4.1	Calories.
1 gram of fat	9.3	"
1 gram of carbohydrate	4.1	"

Their accuracy has been verified by Rubner[1] in the most careful manner.

Rubner,[2] still working in the Munich laboratory, showed that if the diet were increased from a medium to an abundant amount, the metabolism as indicated by the heat production rose. This *dynamic action* resulting from the excessive ingestion of a food-stuff was greatest with protein.

Finally Rubner, in his own laboratory at Marburg, evolved an animal calorimeter which could accurately measure the amount of heat a dog produced in twenty-four hours. The dog was placed within the chamber of the calorimeter, and this chamber was attached to a respiration apparatus, so that the metabolism could be calculated according to the method of Pettenkofer and Voit. From the metabolism the heat production could be estimated. The results were a triumphant demonstration of the truth of the law of the conservation of energy. The amount of heat calculated by Rubner[3] as the quantity that should have been derived from the metabolism of the dog during the day spent in the calorimeter was the amount actually given off by the dog to the calorimeter. The metabolism, the cause of the motions of life, was the source of the heat-loss of the body. The results achieved constitute a final verification of the methods of calculating the total metabolism originated by Pettenkofer and Voit.

An epitome of Rubner's experiments is here presented:

COMPARISON OF ESTIMATED HEAT FROM METABOLISM WITH HEAT ACTUALLY PRODUCED

Food.	Number of Days.	Heat Calculated from Metabolism.	Heat Directly Determined.	Difference in Percentage.
Starvation	5	1296.3	1305.2	−1.42
	2	1091.2	1056.6	
Fat	5	1510.1	1498.3	−0.97
Meat and fat	8	2492.4	2488.0	
	12	3985.4	3958.4	
Meat	6	2249.8	2276.9	−0.42
	7	4780.8	4769.3	+0.43

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[1] Rubner: "Zeitschrift für Biologie," Festschrift zu Voit, 1901, xlii, 261.
[2] Rubner: "Sitzungsberichte der bayer. Akademie," 1885, p. 454.
[3] Rubner: "Zeitschrift für Biologie," 1894, xxx, 73.

Following Rubner, Atwater, at one time a pupil of Voit, with the aid of Rosa, the physicist, constructed a large calorimeter capable of measuring to a nicety the amount of heat given off by a man living in it. This apparatus confirmed Rubner's experiments and has shown that the energy expended by a man in doing any work, such as bicycle-riding, is exactly equal to the energy set free by metabolism in the body. *Ex nihilo nihil fit.*

This apparatus was the product of many years of labor and its cost was borne by the United States Government. Armsby has completed a similar one for use with cattle for the Agricultural Station of the State of Pennsylvania. Benedict with great success has extended Atwater's work in the notable Nutrition Laboratory of the Carnegie Institution in Boston. This is housed in a new building splendidly equipped with apparatus for the simultaneous determination of metabolism and heat production. The work has been still further extended by the construction for the Physiological Laboratory of the Cornell University Medical College in New York City of a small respiration calorimeter[1] suitable for use with babies, dwarfs, and dogs, and of the Sage respiration calorimeter[2] constructed in Bellevue Hospital by the Russell Sage Institute of Pathology for the determination of metabolism in diseased conditions. The two machines have been under the general management of the writer. These elaborate and costly devices prove and confirm the general laws of metabolism in the body enunciated above, through a knowledge of which alone proper systems of nutrition for people under various conditions may be devised (see p. 56). The American Indian when first shown a watch thought it was alive. We, on the other hand, have come to look upon the living organism as a machine. Like the moving locomotive, we burn more if we are to attain a faster speed, or if we are

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[1] Williams: "Journal of Biological Chemistry," 1912, xii, 317.

[2] Riche and Soderstrom: "Archives of Internal Medicine," 1915, xv, 805; Lusk, same "Archives," p. 793.

to keep all parts warm in the winter's cold. In both cases the motion and the heat are derived from the power in the fuel. The casual observer sees the moving train, but the expert engineer alone knows how and why the wheels go round. The physiologist busies himself answering the similar how and why regarding the mechanism of living things.

Before taking up the details of the work we may copy the last general pronouncement of Voit[1] upon the subject of metabolism. It reads:

"The unknown causes of metabolism are found in the cells of the organism. The mass of these cells and their power to decompose materials determine the metabolism. It is absolutely proved that protein fed to the cells is the easiest of all the food-stuffs to be destroyed, next carbohydrates, and lastly fat. The metabolism continues in the cells until their power to metabolize is exhausted. All kinds of influences may act upon the cells to modify their ability to metabolize, some increasing it or others decreasing it. To the former category belong muscular work, cold of the environment (in warm-blooded animals), abundant food, and warming the cells. To the latter, cooling the cells, certain poisons, etc.

"In speaking of the power of the cells to metabolize, I have not meant thereby, as may be seen from all my writings, that the cells must always use energy in order to metabolize, but rather I have understood thereby the sum of the unknown causes of the metabolic ability of the cells—as one speaks of the fermentative 'power' of yeast cells.

"The metabolism of the different food-stuffs varies with the quality and quantity of the food. Protein alone may burn, or little protein and much carbohydrate and fat. I have determined the amount of the metabolism of the various food-stuffs under the most varied conditions. All the phases of metabolism originate from processes in the cells. In a given condition of the cells available protein may be used exclusively if enough be furnished them. If the power of the cells to

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[1] Voit: "Münchener medizinische Wochenschrift," 1902, xlix, 233.

metabolize is not exhausted by the protein furnished, then carbohydrates and fats are destroyed up to the limit of the ability of the cells to do so.

"From this use of materials arise physical results, such as work, heat, and electricity, which we can express in heat units. This is the power derived from metabolism.

"It is possible to approach the subject in the reverse order, that is, to study the energy production (Kraftwechsel) and to draw conclusions regarding the metabolism (Stoffwechsel). It is perfectly possible to say that the requirement of energy in the body or the production of the heat necessary to cover heat loss, or for energy to do work, are controlling factors of the metabolism; since on cooling the body or on working correspondingly more matter is destroyed. But one must not conclude that the loss of body heat and muscular work are the immediate causes of this increased metabolism. The causes lie in the peculiar conditions of the organism, and muscle work and loss of heat are merely factors acting favorably upon those causes, raising the power of the cells to metabolize. In virtue of this more is destroyed, and secondarily the power to work and increased heat production are determined.

"The requirement for energy cannot possibly be the cause of metabolism, any more than the requirement for gold will put it into one's pocket. Hence the production of energy has a very definite upper limit, which is afforded by the ability of the cells to metabolize. If the cells will metabolize no more, then further increase of work ceases even in the presence of direst necessity; and this is also the case with the heat production, even though it were very necessary, and we were likely to freeze.

"I therefore maintain my 'older' point of view, that of pure metabolism, in order to explain the phenomena of nutrition. I am convinced that it is the right way, and that the clearest and most unifying development will be possible as one investigates what substances are destroyed under different circumstances, such as the performance of work, and loss of heat, and how much of the different materials must be fed to maintain the body in condition."

ADDENDUM CONCERNING THE NATURE OF THE FECES

In the historic introduction just given it has been shown that the nitrogen of the urine and feces can be made a measure for the determination of protein metabolism. It is easy to comprehend that urinary constituents, such as urea, uric acid, the purin bases, creatinin, etc., are derived from the metabolism of flesh in the body, whether the flesh be the body's own or that of an animal fed to it. But the intestinal canal where the feces are formed is a long tube open at both ends, through which may pass the nitrogen gas of the air swallowed and indigestible substances such as hair, tacks, etc. In diarrhea the curds of milk, pieces of undigested meat or bread, and large quantities of fat are in evidence. These common observations would seem to justify the popular supposition that normal feces are made up of the undigested residues of the food-stuffs. In truth, however, this is very far from the fact. The feces are chiefly the unabsorbed residues of intestinal excretions.

The collection of the feces for a given period of nutrition is more difficult than the collection of the urine. The urine may be collected every two hours and may fairly represent the protein metabolism of the time, but the feces are normally passed but once a day by a man on a mixed diet, and only once in five days by a dog fed with meat. Furthermore, particles fed to a man are not usually passed in his feces for two or three days. The feces formed during a certain digestive period might therefore leave the body two or three days after the urine was drawn from the bladder. To obtain clear results Voit fed a dog with 60 grams of bones in a preliminary diet eighteen hours before the regular feeding began. These bones yielded a whitish mark in the fecal excretion. All feces subsequent to the mark were attributed to the diet used in the experiment. At the conclusion of the experiment a second diet containing bones was given. The whitish excrement formed from this indicated the end of the feces of the period. For the same purpose Rubner[1] gave milk (2 liters) to a man, the last portion of the milk being taken eighteen hours before the commencement of a period of feeding. The milk feces give a distinct whitish dividing line. A teaspoonful of lampblack may also be readily made use of in man and in animals. Cremer[2] uses freshly precipitated silicic acid (10 to 25 grams mixed with 40 to 100 grams fat) instead of bones. This gives excellent results, as it avoids the albuminoid nitrogen in the bones, and is of great advantage if the calcium or other ash constituents of the feces are to be determined.

In the fundamental experiments Voit found that a fasting dog weighing 30 kilograms excreted 1.88 grams of dry fecal matter per day, containing 0.15 gram of nitrogen. Evidently these starvation feces are not derived from the food, but must be derived from the matter passed from the body into the intestinal canal. An analogous condition is found in the intestinal tract of the newborn infant. The meconium consists principally of the unabsorbed residues of the bile, of glycocholic, taurocholic, and fellic acids, of cholesterin and lecithin, colored by bilirubin or biliverdin. The absence both of putrefaction and the acid of the gastric juice prevents the breaking up and reabsorption of many of these substances, processes which occur soon after birth. The fasting dog of 30 kilograms, mentioned above, excreted 1.88 grams of dry feces, but a fasting dog of 20.3 kilograms may yield 4.3 grams of dry bile solids in twenty-four hours.[3] The ordinary starvation feces therefore cannot consist of the total of the excretions from the body into the digestive tract, but are rather their unabsorbed remainder.

When meat was given, Bischoff and Voit[4] found that the production of feces was not proportional to the amount of

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[1] Rubner: "Zeitschrift für Biologie," 1879, xv, 119.

[2] Cremer: *Ibid.*, 1897, xxxv, 391.

[3] Voit: *Ibid.*, 1894, xxx, 548.

[4] Bischoff and Voit: "Die Ernährung des Fleischfressers," 1860, p. 291.

meat. A compilation of the data given by Friedrich Müller[1] illustrates the average amount of dry feces produced by a dog weighing 35 kilograms after feeding different quantities of meat:

Meat in Grams.	Fecal Solids.	Fecal N.
0	2.0	0.15
500	5.1	0.33
1000	9.2	0.60
1500	10.2	0.66
2000	11.1	0.72
2500	15.4	1.00

The feces had the same pitch-black color as starvation feces and were similar to the 2 grams of feces which would have been produced by the same dog had be been starving. No muscle-fibers and no protein could be detected. It seemed clear that the meat feces differed from the starvation feces mainly in quantity, and that this quantity was larger because the secretions into the intestines had been stimulated by the passing food.

Fat ingested with the meat in moderate quantities had no influence on the feces. Nor had sugar, unless its fermentation produced diarrhea. Bread somewhat increased the volume of the feces, which contained some undigested starch. Here an irritation of the intestinal canal by the bread produced a larger excretion into the intestines.

The source of the feces was further investigated by Hermann,[2] whose work was later elaborated by Fritz Voit.[3] The latter separated a loop of the intestine about a third of a meter long from the rest of the intestine of a starving dog. Both ends of the loop were tied and the loop remained in the abdomen in connection with its normal nerve and blood supply. The two ends of the remaining portion were reunited. After a few days food could be given and the normal excretion of feces took place. After three weeks the animal was killed. It was found that the isolated loop contained a thick, fecal-

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[1] von Müller: "Zeitschrift für Biologie," 1884, xx, 340.
[2] Hermann: "Pflüger's Archiv," 1890, xlvi, 93.
[3] F. Voit: "Zeitschrift für Biologie," 1892, xxix, 325.

like mass. It was found that the dry solids of this mass contained the same percentage of nitrogen as did the feces passed by the dog during the three weeks of the experiment. It was also calculated that the amount of nitrogen excreted through the wall of the intestinal loop was nearly the same per unit of area as the amount of nitrogen in the feces when spread over the surface of the whole of the rest of the intestine. The following table shows this:

	Percentage of N in the Dry Substance.		Grams N from 1 Sq. M. in 24 Hours.	
	Feces.	Content of Loop.	Feces.	Content. of Loop.
Dog I	5.62	5.32	0.28	0.22
Dog III	5.27	6.88	0.25	0.32

The loop contained fat and fatty acids in greater quantity than is normally found in feces, which may indicate a usual reabsorption of these substances.

Fritz Voit has therefore shown that the excretion of substances from an isolated loop of the intestine produces a mass of a similar constitution and of nitrogen output equal to that in the normal intestine of the same animal through which meat and fat were passing. He therefore concludes that the feces are derived principally from the substances excreted through the wall of the intestine. The nitrogen so excreted is as much to be considered a product of protein metabolism as is the nitrogen of urea. It is regretable that very little is known regarding the chemistry of these nitrogenous compounds excreted into the intestine.

It has been seen that the feeding of simple food-stuffs, such as meat, fat, and sugar, scarcely influenced the composition of the feces in the dog. In herbivora we pass to another extreme. Here vast amounts of cellulose are eaten, a great part of which is never disintegrated, but even after long retention in the capacious intestinal tract is passed in the feces. After giving an ordinary feed to a cow one may find as much nitrogen in the feces as in the urine. Under such conditions as these the very voluminous feces evidently do consist largely of the undigested residues of the fodder. Armsby and Fries[1] have shown that only 45 per cent. of the energy contained in hay is of actual use in cattle feeding. The waste in the feces reaches 41 per cent., in the urine 7.25, and in methane gas 6.75 per cent. of the total energy content.

Concerning the fecal production in man, it has been found that Cetti[2] excreted 3.8 grams of dry fecal solids per day during a fast of ten days, Breithaupt 2 grams, and a medical student[3] 2.2 grams, less in reality than would a dog of similar size. Benedict[4] states that he was unable to find any evidence of the formation of feces during a seven-day fast in man.

Rieder[5] gave a man a diet containing starch, sugar, and lard from which a cake was baked. The food contained no nitrogen, but the fecal excretion was 0.54, 0.87, and 0.78 gram of nitrogen per day, contrasting with 0.316 gram from Cetti, 0.113 from Breithaupt, and 0.13 from a medical student during fasting. The food, even though it contains no protein, stimulates the fecal production.

Wallace and Salomon[6] have administered 250 grams of cane-sugar daily to normal persons and to patients suffering from intestinal diarrhea, and have determined the amount of fecal nitrogen during periods of two or three days. The sugar was given in doses of 50 grams dissolved in 300 c.c. of water and flavored with fruits, such as apple and lemon, or with wine. Their results with this diet were as follows:

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[1] Armsby and Fries: Bulletin 101, 1908, Bureau of Animal Industry, U. S. Dept. of Agriculture.

[2] Lehmann, Müller, I. Munk, Senator, Zuntz: "Virchow's Archiv," 1893, Bd. cxxxi, Suppl. Heft.

[3] Johansson, Landergren, Sondén, Tigerstedt: "Skandin. Archiv für Physiologie," 1897, vii, 29.

[4] Benedict: "Influence of Inanition on Metabolism," Carnegie Institution, 1907, p. 345.

[5] Rieder: "Zeitschrift für Biologie," 1884, xx, 378.

[6] Wallace and Salomon: "Medizinische Klinik," 1909, v, 579.

	N in Feces per Day. Grams.
Normal man	0.539
" "	0.380
Tuberculous ulceration of intestine	3.075
" " "	4.186
Cancer of intestine	1.74
" "	1.974
Catarrh of intestine (severe)	1.464
" " "	1.087

It is evident that the quantity of fecal nitrogen eliminated in intestinal diseases is largely increased.

It has been stated that Voit early noticed the occurrence of starch particles in the feces. A large number of experiments have been made to test the digestibility of the various vegetables and cereals. Rubner[1] fed an able-bodied soldier on 3078 grams of variously cooked potatoes daily and found pieces of potatoes in the feces. He notes that an inhabitant of Ireland will eat 4500 grams of potatoes a day. Friedrich Müller[2] writes that after the ingestion of a large quantity of bread the feces may have practically the same composition as bread.

The better understanding of this question of the digestibility of the carbohydrates has come through the work of Prausnitz[3] and his associates, Moeller and Kermauner. Moeller found that no starch appeared in the feces after feeding well-cooked white, rye, and graham bread, rice or potatoes (even when fed in pieces), or legumes when they were prepared in the form of purée. Legumes not in the form of purée, such as string beans eaten as salad, may resist the action of the digestive juices so that the starch contents of the cell are untouched, and the vegetable cells appear in the feces. These facts explain the appearance of bread in the feces if the bread be badly cooked, or if such a "heavy" bread as pumpernickel be eaten. The imperfectly cooked bread contains starch granules whose coverings are impermeable to the digestive juices, as are also many of those in the unbolted rye of pumpernickel.

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[1] Rubner: "Zeitschrift für Biologie," 1879, xv, 146.

[2] Fr. Müller: *Ibid.*, 1884, xx, 375.

[3] Prausnitz: *Ibid.*, 1897, xxxv, 335.

Prausnitz finds that if a man be put on a rice diet and then meat be substituted for most of the rice, the composition of the feces does not vary with the diet. Such feces he calls *normal feces.* They may contain a negligible quantity of fibers of meat (Kermauner) or of cellulose from the rice.

The feces of 6 persons placed alternately on meat and rice diets yielded normal feces, the percentage composition of the dry solids of which was as follows:

COMPOSITION OF FECES ON DIFFERENT DIETS

No.	Person.	Principal Food.	N %.	Ether Extract %.	Ash %.
1	H.	Rice	8.83	12.43	15.37
2	H.	Meat	8.75	15.96	14.74
3	M.	Rice	8.37	18.23	11.05
4	M.	Meat	9.16	16.04	12.22
5	W. P.	Rice	8.59	15.89	12.58
6	W. P.	Meat	8.48	17.52	13.13
7	J. Pa.	Rice	8.25	.....	14.47
8	J. Pa.	Meat	8.16	.....	15.20
9	F. Pi.	Rice	8.70	.....	16.09
10	F. Pi.	Meat	9.05	.....	15.14
11	Vegetarian.	Rice	8.78	18.64	12.01
		Average,	8.65	16.39	13.82

It is seen from this that whether the food solids contain 1.5 per cent. N, as in rice, or ten times that, as in meat, the composition of the feces remains uninfluenced. Normal feces result from the eating of any food which is completely digested and absorbed. In all such cases these feces have the same composition and are derived from the intestinal wall. It is therefore not astonishing that a vegetarian of many years' standing produced the same kind of feces when fed on rice as did the other men. The same quality of feces has been obtained after giving good bread.

In this connection it is interesting to note that the heat value of 1 gram of human feces is very constant whether the person is on a meat diet or a medium mixed diet. Rubner[1] gives the heat value of 1 gram of organic matter in the feces

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[1] Rubner: "Die Gesetze des Energieverbrauchs," 1902, p. 35.

of a man on a meat diet at 6.403 cal., while on a mixed diet 1 gram varies between 6.061 and 6.357 cal. The average fuel value of feces is therefore 6.2 calories per gram of dry organic substance, and this changes only when there is a poor utilization of the food.[1] According to Lorisch,[2] one may calculate the approximate heat value of feces by reckoning the nitrogen therein as protein nitrogen and multiplying the amounts of "protein," "fat," and carbohydrate present by their usual heat value. The sum of these is said to give a rough estimate of the calorific loss through the feces.

After eating pumpernickel, bad bread, or string beans the waste of undigested residues of these substances may appear in the feces, changing its composition and lowering its percentage of nitrogen content.

In general, Prausnitz finds no difference between the digestibility and absorbability of animal and vegetable foods. Meat, rice, and bread from flour are all digested and absorbed. The ordinary feces indicate whether a given food is a small or a great feces builder, not how much or how little food has been used for the organism.

The value in such foods as cabbage, string beans, cauliflower, and the like lies, aside from their flavor, in the fact that their indigestible waste may enhance peristalsis in the intestine. Their food value is small, and if given to those with weak digestions, is dubious. Mendel[3] points out that edible carbohydrate substances, like Iceland moss, agar-agar, Jerusalem artichokes, and inulin, are scarcely attacked by the digestive juices and therefore have little or no direct nutritive function. He[4] also finds that the proteins of mushrooms are not digested in the organism.

The part played by bacteria in the composition of the feces has been variously estimated. Lissauer,[5] working in

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[1] Rubner: v. Leyden's "Handbuch der Ernährungstherapie," 1903, p. 32.
[2] Lorisch: "Zeitschrift für physiologische Chemie," 1904, xli, 308.
[3] Mendel: "Zentralblatt für Stoffwechsel," 1908, iii, 641.
[4] Mendel: "American Journal of Physiology," 1898, i, 225.
[5] Lissauer: "Archiv für Hygiene," 1906, lviii, 145.

Rubner's laboratory, showed that two-thirds of the fecal solids were soluble in alcohol. In the insoluble portion mucin, food protein, and the remnants of cast-off epithelial cells, as well as bacteria were found. When a diet of meat was given to a man food residues were almost entirely wanting in the feces. Though the quantity of bacteria may be of importance in the stools, it is an insignificant factor when compared with the total quantity of food ordinarily ingested. Lissauer finds the following percentages of bacteria in stools of the character noted below:

	Food.	Percentage of Dry Bacterial Substances in Dry Fecal Material.
In Man	Meat	4.3
	Mixed	8.7
	Vegetable	10.5
In Dogs	Meat	5.4
	Potatoes and bread	7.6
In Rabbits		1.0
In Cows		16.7

In man the minimal quantity of bacteria composing the stools was 2.53 per cent., the maximum 13.54 per cent., and the average was 8.7 per cent. of the total solids. Rubner has calculated that 1 gram of dry bacterial substance contains 0.114 gram nitrogen. Making use of these data, Lissauer has prepared the following table to illustrate the part which bacteria may play in the fecal nitrogen elimination of man:

Diet.	Dry Feces Gram.	N Gram.	Bacteria Gram.	Bacterial N Gram.
Meat	17.1	1.12	0.73	0.08
Mixed	30.0	2.9	2.86	0.33

It is evident that the quantity of bacterial nitrogen in the feces is small in comparison with the ordinary intake of nitrogen in the food. Though the feces apparently swarm with bacteria, it should be recalled that 4,000,000,000 weigh only 1 milligram.

It may be added that Osborne and Mendel[1] report that 70 per cent. of the nitrogen of the rat's feces is due to bacteria.

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[1] Osborne and Mendel: "Journal of Biological Chemistry," 1914, xviii, 177.

CHAPTER II

THE ATWATER-ROSA RESPIRATION CALORIMETER

A RESPIRATION CALORIMETER is an apparatus designed for the measurement of the gaseous exchange between a living organism and the atmosphere which surrounds it, and the simultaneous measurement of the quantity of heat produced by that organism.

In 1892 Atwater began work upon a calorimeter which could measure the heat production in man, the first description of which appeared in 1897.[1] The initiative in the undertaking rested with Atwater, whereas the successful completion of the apparatus was largely due to the physicist Rosa. The original Atwater-Rosa calorimeter was combined with a respiration apparatus of the type designed by Pettenkofer, which measured only the carbon dioxid excretion without determining the oxygen intake.

The apparatus represented technical perfection,[2] as was evidenced by the fact that when a measured amount of heat was generated by an electric current within the box it was determined as 100.01 per cent. of the actual value. This test of accuracy is called an *electric check.* Also, when a known quantity of alcohol was oxidized, the carbon dioxid recovered amounted to 99.8 per cent. and the heat to 99.9 per cent. of the theoretic value. This is an *alcohol check.* In experiments with men the work frequently lasted during a period of several days. The method of computation was based on that of Voit and Rubner, *i. e.*, the amount of protein carbon excreted was calculated from the nitrogen excreted in the urine and

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[1] Atwater and Rosa: "Report of the Storrs Agricultural Experiment Station," 1897, p. 212.

[2] Atwater and Benedict: "Memoirs of the National Academy of Sciences," 1902, viii, 231.

feces, this subtracted from the total carbon excreted in the respiration, urine, and feces gave the *total non-protein carbon* or that attributable to carbohydrate and fat. It was assumed that all the carbohydrate ingested was oxidized and that after deducting this amount the excess of non-protein carbon was derived from the metabolism of fat. In this way the calories from protein, carbohydrate, and fat were computed. The validity of this method is shown in the work of Atwater and Benedict by the average results per day of forty days of experimentation with three different individuals who took an ordinary mixed diet:

	Calories.
Indirect calorimetry	2717
Direct calorimetry	2723
Difference	0.2 per cent.

Atwater was not content to omit the determination of oxygen, and turned his attention to this important problem. As already explained (p. 29), the quantity of oxygen required in metabolism depends on the kind of material oxidized in the organism, and the relation between the amount of oxygen absorbed and carbon dioxid eliminated depends on the same factor. The ratio of the *volume* of carbon dioxid expired to the *volume* of oxygen inspired during the same interval of time was called by Pflüger the *respiratory quotient.*

It was known to Lavoisier that any volume of oxygen uniting with carbon produced the same volume of carbon dioxid. Since the volume of oxygen inspired was found in his experiments to be larger than that of the expired carbon dioxid, Lavoisier concluded that a portion of the inspired oxygen must have been used to oxidize hydrogen in the production of water. Under these circumstances the $\frac{\text{Volume } CO_2}{\text{Volume } O_2}$ would be less than unity. The carefully executed experiments of Regnault and Reiset, published in 1849, showed that the value of the respiratory quotient depended on the nature of the food given and not on the species of animal. They found that the respiratory quotient might vary in the same animal from 1.02 to 0.64, and that it varied with the kind of food taken, but was constant with the same food. When fowls were fed with corn or dogs with bread, respiratory quotients of 1.02 and 0.93, respectively, were obtained. The quotients were lower when a meat diet was given and still lower than this when the animal fasted. The low quotients during inanition were obtained alike with herbivorous and carnivorous animals, which indicated to Regnault and Reiset that these animals lived upon their own flesh under conditions not unlike those existing when a meat diet was taken.

Turning now to modern analysis, it is evident that when carbohydrate, in which hydrogen and oxygen are always present in the proportion to form water, is oxidized, the respiratory quotient will be unity. One may express the process thus:

$$C_6H_{12}O_6 + 6O_2 = 6CO_2 + 6H_2O$$

Since equal volumes of gases at the same temperature and pressure contain equal numbers of molecules (Law of Avagadro, 1811) it is evident from the above formula that one volume of oxygen absorbed produces one volume of carbon dioxid during carbohydrate combustion. Hence, for carbohydrate the R. Q. = *1.00.*

When fat is oxidized oxygen is utilized not only for the production of carbon dioxid, but also for the oxidation of hydrogen, forming water.

This is evident from the following formula:

$$C_3H_5(O_2C.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.\text{-}$$
$$CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_3)_3$$

Tripalmitin.

If one deducts the intramolecular water from tripalmitin one obtains the following:

Tripalmitin	$C_{51}H_{98}O_6$
Deduct intramolecular H_2O	$H_{12}O_6$
Leaving for oxidation	$C_{51}H_{86}$

This on oxidation yields:

$$2(C_{51}H_{86}) + 145O_2 = 102CO_2 + 86H_2O$$

$$\text{R. Q.} = \frac{102 \text{ volumes } CO_2}{145 \text{ volumes } O_2} = 0.703$$

Edible fats are usually mixtures of various simple fats, consisting for the most part of tripalmitin, tristearin, and triolein, all of which require nearly the same quantity of oxygen for oxidation. Lehmann, Müller, Munk, Senator, and Zuntz[1] analyzed the respiratory quotient which should be obtained from lard as follows:

1 gram lard	= 0.765 g. C	+ 0.119 g. H + 0.116 g. O
Deduct intramolecular water		0.0145 g. H + 0.116 g. O
	0.765 g. C	+ 0.1045 g. H
Required for oxidation	2.040 g. O	+ 0.836 g. O
	2.805 g. CO_2	+ 0.9405 g. H_2O

As the weight of the oxygen molecule is to that of carbon dioxid as 8 is to 11, the respiratory quotient is deduced from the relative weights as follows:

$$\text{R. Q.} = \frac{2.805 \text{ g. } CO_2}{2.876 \text{ g. } O_2} \times \frac{8}{11} = 0.710$$

Zuntz[2] later slightly changed the oxygen value so that the calculated quotient was *0.707*. A still more recent computation by Zuntz[3] for human fat shows a respiratory quotient of 0.713. The respiratory quotient of fat is, therefore, very constant.

The respiratory quotient for protein is, for the most part, the resultant of the oxidation of the various amino-acids of which protein is composed (see p. 77). This quotient, as calculated by Zuntz, is based upon the careful analytic data

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[1] Lehmann, Müller, Munk, Senator, and Zuntz: "Virchow's Archiv," 1893, cxxxi, Suppl. Bd., p. 131.

[2] Zuntz: "Pflüger's Archiv," 1897, lxviii, 201.

[3] Zuntz: "Zuntz und Loewy's Lehrbuch der Physiologie des Menschen," 2d edition, Leipzig, 1913, p. 644.

prepared by Rubner, already described. Zuntz, however, substracted the fat in the feces from the material attributable to protein metabolism. A recent computation by Loewy[1] is as follows:

100 grams meat protein contain:					
	52.38 g. C	7.27 g. H	22.68 g. O	16.65 g. N	1.02 g. S
of which is eliminated—					
in the urine:	9.406 g. C	2.663 g. H	14.099 g. O	16.28 g. N	1.02 g. S
in the feces:	1.471 g. C	0.212 g. H	0.889 g. O	0.37 g. N	
leaving a residuum for the respiratory process of—					
	41.50 g. C	4.40 g. H	7.69 g. O		
deduct intra-molecular water:		0.961	7.69		
	41.50 g. C	3.439 g. H			

These quantities of carbon and hydrogen would require 138.18 grams of O_2 and produce 152.17 grams of CO_2. Since 1 gram of oxygen is the equivalent of 0.699 liter and 1 gram of carbon dioxid amounts to 0.5087 liter, the R. Q. would be $\frac{77.39 \text{ liters } CO_2}{96.63 \text{ liters } O_2} = 0.801$. From these data it may be calculated that for every gram of urinary nitrogen derived from protein 8.45 grams of oxygen are required for the oxidative process and 9.35 grams of carbon dioxid are eliminated in virtue of such oxidation.

In consequence of this, one may estimate the substances oxidized in the organism by deducting from the total elimination of carbon dioxid the quantity derived from protein (grams urinary N × 9.35), and from the total oxygen absorbed that required to oxidize protein (grams urinary N × 8.45). From the figures so obtained one determines the *non-protein* R. Q. From this the part played by fat and carbohydrate in metabolism may be computed. For when fat alone is oxidized the quotient will be 0.707, and when carbohydrate is oxidized it will be 1.00. Quotients which are intermediary between these two indicate that mixtures of the two materials are being destroyed (see p. 61). Knowing the quantities of these gases, their relative volumes (the R. Q.), and also the nitrogen elimination, it is possible to calculate exactly what amounts

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[1] Loewy: "Oppenheimer's Handbuch der Biochemie," 1911, iv, 1, 279.

of protein, carbohydrate, and fat have been oxidized during the period of experimentation.

The significance of the Non-protein Respiratory Quotient as regards the heat value of 1 liter of oxygen, and the relative quantity in calories of carbohydrate and fat consumed. (Modified from Zuntz and Schumburg.)

R. Q.	CALORIES FOR 1 LITER O_2.		CARBOHYDRATE.	FAT.
	Number.	Logarithm.		
			Per Cent.	Per Cent.
0.707	4.686	0.67080	0	100
0.71	4.690	0.67116	1.4	98.6
0.72	4.702	0.67231	4.8	95.2
0.73	4.714	0.67346	8.2	91.8
0.74	4.727	0.67460	11.6	88.4
0.75	4.739	0.67574	15.0	85.0
0.76	4.752	0.67688	18.4	81.6
0.77	4.764	0.67801	21.8	78.2
0.78	4.776	0.67913	25.2	74.8
0.79	4.789	0.68024	28.6	71.4
0.80	4.801	0.68136	32.0	68.0
0.81	4.813	0.68247	35.4	64.6
0.82	4.825	0.68358	38.8	61.2
0.83	4.838	0.68469	42.2	57.8
0.84	4.850	0.68578	45.6	54.4
0.85	4.863	0.68690	49.0	51.0
0.86	4.875	0.68800	52.4	47.6
0.87	4.887	0.68910	55.8	44.2
0.88	4.900	0.69019	59.2	40.8
0.89	4.912	0.69128	62.6	37.4
0.90	4.924	0.69230	66.0	34.0
0.91	4.936	0.69343	69.4	30.6
0.92	4.948	0.69450	72.8	27.2
0.93	4.960	0.69557	76.2	23.8
0.94	4.973	0.69664	79.6	20.4
0.95	4.985	0.69771	83.0	17.0
0.96	4.997	0.69878	86.4	13.6
0.97	5.010	0.69985	89.8	10.2
0.98	5.022	0.70092	93.2	6.8
0.99	5.034	0.70199	96.6	3.4
1.00	5.047	0.70307	100.0	0.0

The R. Q., therefore, ranges from 0.707 for fat to 1.00 for carbohydrate. Exceptions may be noted under conditions involving the conversion of carbohydrate into fat in which case the quotient exceeds unity (see p. 306) and in severe diabetes, when the quotient may be less than 0.707 (see p. 470).

From this analysis of the oxidative process associated with the destruction of carbohydrate, fat, and protein in the organism, it is possible to compute the heat value of the respiratory gases when the various substances are oxidized. This knowledge may be compressed into the following table given by Loewy[1]:

1 Gram Substance.	O_2 absorbed.	CO_2 formed.	R. Q.	Calories.	Calories.	
					1 Liter O_2.	1 Liter CO_2.
	C.c.	C.c.				
Protein......	966.3	773.9	0.801	4.316	4.485	5.579
Fat.........	2019.3	1427.3	0.707	9.461	4.686	6.629
Starch.......	828.8	828.8	1.000	4.182	5.047	5.047

Based upon the analytic figures given for protein, it may be computed that:

1 gram urinary nitrogen = 26.51 calories.

The calories derived from the oxidation of fat and carbohydrate given by Zuntz and Schumburg[2] are reproduced on p. 61.

An example of the calculation of indirect calorimetry may be of value as an illustration. The subject was a dog weighing 12.75 kilograms and the period was one hour in duration. The calories directly determined by the calorimeter are also given:

	CO_2 Grams.	O_2 Grams.	R. Q.	Urine N Grams.
Respiratory exchange	6.75	6.17	0.79	0.136
Deduct protein (0.136 × 9.35) =	1.27	(0.136 × 8.45) = 1.15		
Non-protein	5.48	5.02 (= 3.51 liters)	0.79	

	Calories Indirect.	Calories Direct.
Protein calories (0.136 grams N × 26.51)	= 3.60	
Non-protein calories (3.51 liters O_2 × 4.789*)	= 16.83	
	20.43	20.92

Difference, 2.5 per cent.

* Calorific value of 1 liter O_2 when R. Q. = 0.79.

The same method is employed in the calculations of the metabolism of man.

[1] For slightly different values consult Benedict and Talbot: "The Gaseous Metabolism of Infants," Carnegie Institution, Publication 201, 1914, p. 26.

[2] Zuntz and Schumburg: "Studien zu einer Physiologie des Marsches," Berlin, 1901, p. 361.

In a series of twenty-two different experiments with a dog Murlin and Lusk[1] obtained the following results:

	CALORIES.
Indirect calorimetry	2244
Direct calorimetry	2230
Difference	0.6 per cent.

In fourteen of the twenty-two experiments the individual error was less than 2 per cent.

The following is a description of the principles of an Atwater-Rosa respiration calorimeter with the improvements added by Benedict,[2] Williams,[3] and others, which has been adapted for the use of patients in Bellevue Hospital:[4]

PRINCIPLE OF THE ATWATER-ROSA-BENEDICT RESPIRATION CALORIMETER[5]

The apparatus is divided into two functional parts, one for measuring the gaseous exchange, the other for measuring the heat production of the subject. A schematic presentation is here given (Fig. 1).

The Gas Analysis.—The inner lining of the apparatus presents an air-tight copper box having a capacity of 1123 liters. One end of the box, through which the patient lying on the bed is admitted, may be closed with a glass plate by means of wax. The air within the box is purified by drawing it out of an opening in the box through a rubber tube and forcing it by means of a rotary blower through a system of *absorbers*, whence it returns again to the box by another rubber tube. It passes (see diagram) first through sulphuric acid (1), which removes the water, then through moist soda lime (2), which removes the carbon dioxid, and next through sulphuric acid (3), which absorbs the moisture taken from the soda lime. If the bottles be previously weighed, the gain in weight of 1 represents water absorbed, and the gain in weight of 2 plus 3 equals the carbon dioxid absorbed. By this method the water and carbon dioxid produced by a man are taken from the air, while oxygen within the chamber is being absorbed by the man himself. This causes a diminution in the volume of the contents of the box. In order to replace the oxygen used, oxygen is automatically fed into the system from an oxygen cylinder which may be weighed before and after the period. The automatic feeding of oxygen into the box is accomplished by means of a spirometer whose interior is connected with the interior of the calorimeter chamber. As the volume of the

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[1] Murlin and Lusk: "Jour. of Biological Chemistry," 1915, xxii, 17.

[2] Benedict and Carpenter: Carnegie Institution of Washington, 1910, Publication 123.

[3] Williams: "Jour. of Biological Chemistry," 1912, xii, 317.

[4] Riche and Soderstrom: "Archives of Internal Medicine," 1915, xv, 805.

[5] Lusk: "Archives of Internal Medicine," 1915, xv, 793.

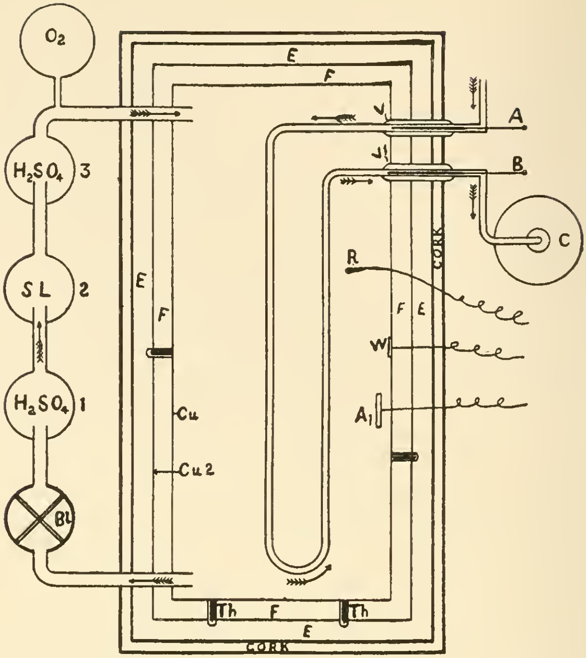

Fig. 1.—Schematic diagram of the Atwater-Rosa-Benedict respiration calorimeter.

Ventilating System:
- O_2, Oxygen introduced as consumed by subject.
- 3, H_2SO_4 to catch moisture given off by soda lime.
- 2, Soda lime to remove CO_2.
- 1, H_2SO_4 to remove moisture given off by patient.
- Bl, Blower to keep air in circulation.

Indirect Calorimetry:
- Increase in weight of H_2SO_4 (1) = water elimination of subject.
- Increase in weight of soda lime (2) + increase in weight of H_2SO_4 (3) = CO_2 elimination.
- Decrease in weight of oxygen tank = oxygen consumption of subject.

Heat-absorbing System:
- A, Thermometer to record temperature of ingoing water.
- B, Thermometer to record temperature of outgoing water.
- V, Vacuum jacket.
- C, Tank for weighing water which has passed through calorimeter each hour.
- W, Thermometer for measuring temperature of wall.
- A_1, Thermometer for measuring temperature of the air.
- R, Rectal thermometer for measuring temperature of subject.

Direct Calorimetry:
- Average difference of A and B × liters of water + (gm. water eliminated × 0.586) ± (change in temperature of wall × hydrothermal equivalent of box) ± (change of temperature of body × hydrothermal equivalent of body) = total calories produced.

Th, thermocouple; Cu, inner copper wall; Cu_2, outer copper wall; E, F, dead air-spaces.

air in the box decreases, the spirometer falls until a certain point is reached, at which an electric contact releases a clamp, which allows oxygen from the oxygen cylinder to enter the box, causing the spirometer to rise, break its electric contact, and clamp off the oxygen supply. So sensitive is the spirometer to the movement of the patient that a device called a "work adder" has been attached to it, which records the subject's movements.

At the beginning of an hourly period of experimentation an observer at the table calls "time." At this instant the rotary blower is stopped, the air current switched so as to pass through a new set of weighed absorbers, and then the rotary blower is started again. At the word "time" an operator also turns a pet-cock which cuts off the respiratory chamber from the spirometer cylinder, which is then filled, always to a given point, with oxygen from the oxygen cylinder. The pet-cock is now opened and a freshly weighed oxygen cylinder is placed in the position of the other, which is removed. Repeating these procedures an hour later, one may determine by difference in weight the gain of water and carbon dioxid by the absorbers and the loss of oxygen by the cylinder. The figures are subject to corrections due to (1) gain or loss of water or carbon dioxid content in the box itself during the period, which gain or loss must be added to or subtracted from the increase in weight of the absorber system. This gain or loss of water and carbon dioxid in the box also affects the volume of the air in the box and, therefore, the quantity of oxygen admitted, as do, in addition (2), a change in temperature within the box and (3) a change in barometric pressure. These corrections must be made in order to determine whether oxygen is to be added or subtracted from the quantity which has been furnished from the oxygen cylinder. The result gives the quantity of oxygen which the man has absorbed. It is apparent that all the errors of determination fall on the oxygen, and yet the exactness of the method is witnessed by the close approximation in alcohol check experiments of the theoretic and actual values for oxygen consumed.

If a person in the calorimeter moves even the arm during the critical moments just before "time" is called, the increased local heating of the air may cause the spirometer to rise to a considerable height, of which the air thermometers inside the box fail to make compensatory record, and the oxygen determination will be too low in that hour and too high in the next.

Analysis of the air in the interior of the chamber is made just before the beginning of each hour by passing 10 liters of air from the box through three **U** tubes containing, respectively, sulphuric acid, soda lime, and sulphuric acid, then through a Bohr gas-meter, and back into the box again. This is called the "residual analysis."

Under the conditions present in the respiration apparatus carbon dioxid is measured with the greatest ease and accuracy. Oxygen is also measured with accuracy if the person within the box lies perfectly quiet for ten minutes before the end of the period, whereas water production is the least accurate of all the determinations on account of the varying hygroscopic condition of the walls, bedding, and other surfaces within the closed spaces of the apparatus.

The Measurement of Heat Produced.—Roughly speaking, one-quarter of the heat eliminated by a man is present in the water vapor which is absorbed by the first sulphuric acid bottle on the absorber table. At 20° C. 0.586 calories are contained as latent heat in 1 gram of vaporized water.

The rest of the heat loss takes place by radiation and conduction. It is this heat which is measured by the calorimeter itself. The mechanism of the calorimeter is essentially twofold. In the first place, there is no heat loss through the walls of the apparatus, and, secondly, the heat produced by a man within is removed from the chamber by a current of cold water flowing through copper tubes suspended from the upper wall of the chamber. If the walls allowed no heat to pass, it is obvious that without the cooling effect of the water-pipes the temperature of the air in the box would soon attain the temperature of the human body instead of being about 23° C., at which it is usually held. The apparatus is therefore a constant-temperature, water-cooled calorimeter. It is evident that if no heat is allowed to pass through the walls of the calorimeter, then the heat produced within the chamber will be removed in the current of cold water flowing through the heat-absorbing pipes inside the chamber of the apparatus. If the temperatures of the ingoing and of the outgoing water are known and the quantity of water which has passed through the heat-absorber during an hour is measured, the quantity of heat carried away in the current of water can be accurately determined. For example, if the difference between the temperature of the ingoing and outgoing water is 2.50 degrees, and 20 liters of water have passed through the heat absorber in one hour, then 50 calories of heat have been carried away from the apparatus during the period. If the temperature of the walls within the apparatus has undergone a change this value is subject to corrections, but otherwise the total heat elimination of the person is measured by the 50 calories so determined plus the heat value of water vaporized during the hour.

To obtain an even flow of water through the heat-absorber the water is supplied from a constant-level tank placed above the calorimeter. To obtain ingoing water of an even temperature Williams passed the previously ice-cooled water current through a Gouy temperature regulator and then through a current regulator designed by himself. These improvements allow the ingoing water to enter the calorimeter at a temperature which may not vary more than 0.02° C. during hours of experimentation and, for the first time, permit the exact measurement of small quantities of heat in this type of apparatus. The temperatures of the ingoing and outgoing water are taken every four minutes by electric resistance thermometers and are read in connection with a galvanometer and Kohlrausch bridge on an observer's table. The quantity of the water-flow is determined by weighing; the water is diverted at the call of "time," so that the exact quantity for the hour is collected in a previously weighed receptacle.

Having learned how the heat produced within the apparatus is carried away, the problem of how to prevent loss of heat through the walls of the chamber remains to be discussed. This was accomplished through a device introduced by Rosa. The calorimeter is constructed of three walls, an inner copper wall which has already been described as the lining of the respiration chamber, an outer copper wall separated from the inner wall by a space of dead air, and an insulating wall (made of two layers of "compo-board," the

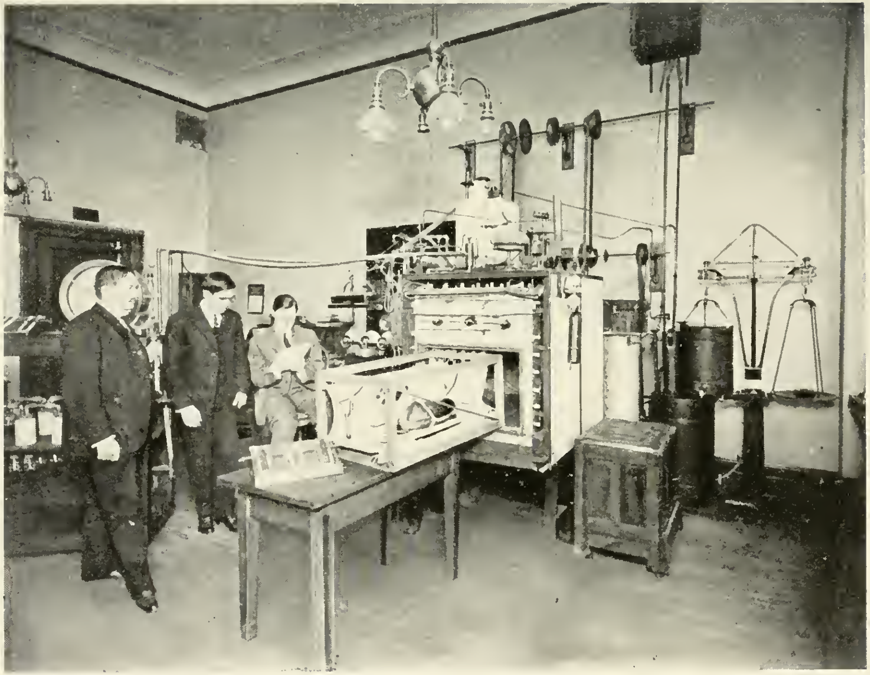

Fig. 2.—This figure shows a small respiration calorimeter built by H. B. Williams for the Physiological Laboratory, Cornell Medical College, New York City. A dog, wearing a bandage which holds a rectal thermometer in place, is shown lying on a cot suspended from a frame which may at any time be slid into the open chamber of the calorimeter. This accomplished, the front is then sealed. The animal respires within the chamber; the water and carbonic acid which he eliminates are removed by circulating the air through absorbing chemicals, and fresh oxygen is admitted automatically to replace the oxygen absorbed by the animal. The heat produced by the dog is removed by a current of water flowing through a system of pipes within the calorimeter.

space between them being filled with cork), which insulating wall is separated from the outer copper wall by a second space containing dead air. It is obvious that if the inner and outer copper walls of the calorimeter have the same temperature there will be no exchange of heat between them. Therefore, to prevent a gain or loss of heat by the inner wall, it is necessary to maintain the outer wall always at exactly the same temperature as the inner wall, under which circumstances the latter cannot gain or lose heat to its neighbor.

In order to detect differences in temperature between the outer and inner walls Rosa arranged thermo-couples in series between the two walls. In this fashion the top, sides, and bottom of the box are successively tested every four minutes by an operator at the observer's table to determine whether there is any difference in temperature between the outer and inner walls. If the outer wall is found to have a different temperature from the inner wall, its temperature is brought to that of the inner wall by the following device: A cooling current of water runs through pipes between the insulating and outer copper wall, and in this same space, along the line of the pipes, run "Therlo" resistance wires carrying an electric current for the warming of this interspace (see Fig. 2). By varying the intensity of the electric currents which severally supply the spaces to top, sides and bottom, the temperature of these spaces can be so controlled as to heat or cool the outer copper wall and maintain it at exactly the same temperature as the inner copper wall. This is the effective system which prevents a loss or gain of heat through the wall of the calorimeter.

Resistance thermometers are attached to the inner walls of the calorimeter, and if the temperature of the walls rises or falls between the beginning and end of the experiment, a correction must be made. It has been found that 19 calories are absorbed by the Sage calorimeter when the inner wall rises 1 degree. Conversely, 19 calories are given up by a fall of 1 degree. This is the *hydrothermal equivalent* of the box.

The temperature of the air entering the box from the absorbing table is always heated to exactly the same temperature as the air leaving the box.

Finally, an electric resistance thermometer inserted 10 or 12 cm. into the rectum of the person in the calorimeter gives information regarding the retention or loss of heat in his organism. The specific heat of a man is assumed to be 0.83, that is to say, 0.83 calorie raises 1 kilogram 1 degree. If, therefore, the body temperature of a man weighing 70 kilograms rises or falls 1 degree, the quantity of heat lost or gained by the body will be 70 × 0.83, or 58.1 calories. This is on the assumption that the rise of body temperature is everywhere the same as takes place in the rectum, a supposition which, unfortunately, is not always true (see p. 132).

The accompanying scheme (on p. 68) gives the details regarding the employment of the three individuals who conduct a calorimeter experiment.

It may be added that special care has been taken to make the appearance of the calorimeter attractive to the eye, and that the spirit of the small ward in connection with the calorimeter work has been such that the patients have considered themselves especially fortunate when chosen for the diversion offered by a morning's occupancy of the apparatus.

SCHEME OF EMPLOYMENT OF OBSERVERS IN A CALORIMETER EXPERIMENT

PERIOD OF OBSERVATION.	OBSERVER 1, AT ELECTRIC CONTROL TABLE.	OBSERVER 2, IN CHARGE OF EXPERIMENT.	OBSERVER 3, CALCULATOR.
Eight minutes before.	Brings walls into exact thermal equilibrium.	Signals subject to lie absolutely quiet.	Starts passing first 10-liter sample of residual air through **U** tubes.
Five minutes before.	....	Starts kymograph record of movements of spirometer.	
Four minutes before.	....	....	Finishes first and starts second residual.
One-half minute before.	Takes final reading of air, walls, and rectal temperature.	Sets barometer.	Finishes second residual.
At "Time."	Presses button which diverts stream of water from weighing tank.	Shuts spirometer off from box. Fills to standard level from oxygen tank.	Stops ventilating current of air. Turns valve to pass air through newly weighed absorbers. Starts ventilating current.
Immediately after "Time."	Starts taking readings every four minutes of ingoing and outgoing water, of air, walls, rectal, and surface thermometers. Reads and adjusts temperature of top, sides, and bottom of calorimeter, of the ingoing air and water every four minutes, or oftener if necessary.	Records and sets work-adder. Signals to subject that he may move. Weighs oxygen tank and connects with box again. Weighs sulphuric and soda lime bottles. Connects them up again and tests for leaks. During remainder of hour counts pulse, inspects valves for leaks, adjusts temperature of room, watches subject, etc.	Weighs water tank which has received all the water from the heat absorber during the past hour. Diverts stream of water to this tank again. Records barometer. Weighs residual. Calculates results of the hour just finished.

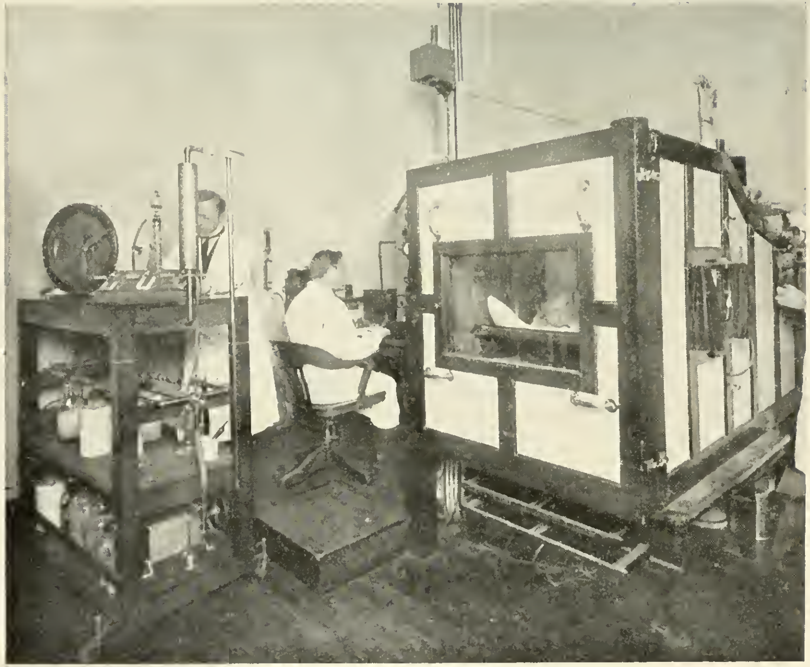

Fig. 3.—Showing the respiration calorimeter of the Russell Sage Institute of Pathology which is affiliated with the Second (Cornell University) Division of Bellevue Hospital, New York City. From left to right, observer 3 is at the "absorber table"; the residual U tubes and the 10-liter meter are on top; the "absorbers" of CO_2 and H_2O are on the middle shelf, and the "blower" on the lower shelf. Observer 1 is at the electric control table. Observer 2 is filling the spirometer with his right hand from an oxygen cylinder he is touching with his left.

CHAPTER III

STARVATION

NUTRITION may be defined as the sum of the processes concerned in the growth, maintenance, and repair of the living body as a whole or of its constituent organs.

An intelligent basis for the understanding of these processes is best acquired by a study of the organism when it is living at the expense of materials stored within itself, as it does in starvation.

Starvation or hunger is the deprivation of an organism of any or all the elements necessary to its nutrition. Thus when carbohydrates and fats only are eaten, protein hunger ensues. If the body is deprived of water or of calcium, thirst or calcium hunger, as the case may be, follows. Complete starvation occurs when all the required elements are inadequate. A fasting dog to whom no food or drink is offered does not undergo starvation in this sense, for the metabolized tissue furnishes enough water for the urine and respiration. There is also no water hunger in a dog when meat is ingested, for the meat contains enough water to dissolve the end-products of its metabolism in the urine. Dogs and cats have no sweat-glands in the skin except in the pads of their feet. They therefore are not so susceptible to water hunger as is man, whose body surface is constantly losing moisture.

A true picture of water hunger is presented by Straub,[1] who gave a dog dry meat powder mixed with fat. Under these circumstances water is withdrawn from the tissues to dissolve the urea formed. He found that muscles may lose 20 per cent. of their water content without pathologic manifesta-

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[1] Straub: "Zeitschrift für Biologie," 1899, xxxviii, 537.

tions, although withdrawal of water somewhat increased the protein metabolism. The experiment could not be carried to the point of death from thirst, for after a few days the food was regularly vomited, on account of the decreased flow of the digestive secretions and an altered condition of the intestinal canal. The non-absorption of the meat powder threw the body on the resources of its own tissue, and this form of starvation, as has been shown, does not constitute water hunger.

Rubner[1] finds that starving pigeons die of thirst in four to five days, while those allowed only water live twelve days. Water hunger is, therefore, more quickly fatal than starvation when water is allowed. Under the usual conditions of so-called starvation experiments water is freely allowed, so that water hunger does not enter as a factor into the following discussion.

If water be available, the organism obtains the energy necessary for its continued existence from the destruction of its own store of protein and fat. After a variable length of time the organism succumbs. Exposure to cold greatly hastens the end. What is ordinarily called death from starvation is often really death from exposure.

Boldireff[2] described rhythmic movements occurring in the empty stomach, and Cannon and Washburn[3] have called attention to the intimate association of these contractions with the pangs of hunger. The subject has been studied in detail by Carlson[4] in observations upon a boy with a gastric fistula. Twenty-four hours after a meal the stomach exhibited two types of rhythmic movements: (1) relatively feeble, but continuous contractions at the rate of three per minute, and (2) relatively strong contractions of the fundus, the true hunger-pains. The amplitude of these latter contractions shows a

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[1] Rubner: v. Leyden's "Handbuch der Ernährungstherapie," 1903, p. 53.

[2] Boldireff: "Archives des sciences biologiques," 1905, xi, 1.

[3] Cannon and Washburn: "American Journal of Physiology," 1911–12, xxix, 441.

[4] Carlson: "American Journal of Physiology," 1912–13, xxxi, 151.

close correspondence with the intensity of the sense of hunger simultaneously registered. During strong contractions the knee-jerk was found to be exaggerated, indicating an increased tonus of the nervous system, and there was a great instability of vasomotor tone. Carlson suggests that this close association of the hunger-pains with the vasomotor center may be the cause of the faintness occurring in starvation. The hunger contractions and, in consequence, the hunger pangs are inhibited by: (1) the stimulation of the gustatory nerves through sweet, bitter, salt, and acid substances; (2) chewing any kind of substance, be it well or ill flavored or tasteless; (3) smoking; (4) swallowing movements. Water, coffee, tea, beer, wine, and brandy when taken into the stomach inhibit the movements and relieve the sense of hunger, though water is least effective in this regard.

Succi has fasted several times for thirty days. Dr. Tanner, an American physician, for forty days; and Merlatti, in Paris, for fifty days. Succi took laudanum in considerable quantity to stay the pain in his stomach, while Merlatti took only water.[1] The effect of fasting on the spirits of the faster varies with the individual. Usually there is a loss of buoyancy of spirit, a decreased desire to work, and a decrease in the actual power of working. Succi, however, was capable of considerable exertion, such as walking and riding, without ill effects. A dog does not manifest the same depression as is seen in man. Dogs may be starved several days before they are run in a hunt. One of the longest fasts on record is that of Kumagawa's[2] dog, which died on the ninety-eighth day. This dog was reduced in weight from 17 to 5.96 kilograms, a loss of 65 per cent.

A yet longer fast has been reported by Hawk,[3] in which a dog fasted from February 6th to June 2d, a period of 117 days, 700 grams of water having been administered daily. The

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[1] Luciani: "Das Hungern," 1890, p. 28.

[2] Kumagawa and Miura: "Archiv für Physiologie," 1898, p. 431.

[3] Howe, Mattill, and Hawk: "Journal of Biological Chemistry," 1912, xi, 103.

dog remained in "good spirits" during the whole fast, although its weight fell from 26.3 to 9.76 kilograms. There was no indication of a "premortal rise" in the nitrogen elimination in the urine. During the first four days of fasting the average nitrogen elimination in the urine was 6.23 grams or 0.23 gram per kilogram of body weight, and during the last four days it averaged 2.44 grams or 0.23 gram per kilogram. The dog then passed the summer upon a Kansas farm, fully regained his former weight, and in the autumn was reported to be in better physical condition than at the commencement of his fast. A second or "repeated fast" was then initiated which lasted 104 days with no harmful results.

The day to day history of the starving organism must now be considered.

In the first days the amount of protein metabolized depends upon the two factors, the glycogen content of the individual and the quantity of protein ingested before the starvation period. The influence of the first factor was shown by Prausnitz.[1] Fifteen individuals (mostly medical students who were taking a course of instruction in the laboratory) fasted for sixty hours. The first day's urine was collected beginning after twelve hours of fasting. The second day's urine contained in 12 cases more nitrogen than that of the first day of starvation. The lower protein destruction on the first starvation day must have been due to the continued use of sugar from the glycogen supply. It is known that the combustion of sugar considerably reduces the protein metabolism, so the second day and not the first of starvation should be taken as the basis of the fasting protein metabolism.

This influence of glycogen metabolism on that of protein during the first and second days of fasting is beautifully shown in experiments by Benedict[2] (see also p. 89).

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[1] Prausnitz: "Zeitschrift für Biologie," 1892, xxix, 151.

[2] Benedict: "The Influence of Inanition on Metabolism," Carnegie Institution of Washington, 1907, Bulletin No. 77.

INFLUENCE OF GLYCOGEN METABOLISM ON THAT OF PROTEIN IN FASTING. WEIGHTS IN GRAMS

Individual.	First Day.			Second Day.		
	Glycogen Metabolized.		N Eliminated.	Glycogen Metabolized.		N Eliminated.
	Total.	Per Kg.		Total.	Per Kg.	
S. A. B.	181.6	3.15	5.84	29.7	0.52	11.04
S. A. B.	135.3	2.31	10.29	18.1	0.31	11.97
S. A. B.	64.9	1.09	12.24	23.1	0.39	12.45
H. C. K.	165.6	2.33	9.39	44.7	0.64	14.36
H. R. D.	32.8	0.59	13.25	41.6	0.76	13.53

It is evident that where there is an abundant glycogen reserve the protein metabolism is reduced by the oxidation of carbohydrates, but where there is little glycogen to draw upon the protein metabolism is high even on the first day of starvation.

The second factor, or the influence of the previous meat ingestion, is especially dominant in dogs. (For effect on man see p. 275.) Voit[1] fed a dog weighing 35 kilograms with different quantities of meat and noticed the effect on urea elimination during subsequent starvation. The results were as follows:

INFLUENCE OF PREVIOUS DIET ON UREA ELIMINATION IN STARVATION

	Grams of Urea Excreted During Starvation Following Various Diets.				
	Meat, 2500 G.	Meat, 1800 G.; Fat, 250 G.	Meat, 1500 G.	Meat, 1500 G.	Bread.
Last food day	180.8	130.0	110.8	110.8	24.7
1st fasting day	60.1	37.5	29.7	26.5	19.6
2d " "	24.9	23.3	18.2	18.6	15.6
3d " "	19.1	16.7	17.5	15.7	14.9
4th " "	17.3	14.8	14.9	14.9	13.2
5th " "	12.3	12.6	14.2	14.8	12.7
6th " "	13.3	12.8	13.0	12.8	13.0
7th " "	12.5	12.0	12.1	12.9	
8th " "	10.1	...	12.9	12.1	...
9th " "	...	...	...	11.9	
10th " "	...	...	...	11.4	

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[1] Voit: "Zeitschrift für Biologie," 1866, ii, 307.

It is evident from this that on the sixth day of starvation the urea elimination was the same in all cases, or about 13 grams of urea per day. Voit deducted the 12 grams from what he had found for the first days and obtained the grams of urea which were derived from the previous food, as follows:

UREA ELIMINATION IN STARVATION ATTRIBUTABLE TO PREVIOUS DIET

	Meat, 1500 G.	Meat, 1800 G.; Fat, 250 G.	Meat, 1500 G.	Meat, 1500 G.	Bread.
(Last food day)..........	(168.8)	(118.0)	(98.8)	(98.8)	(12.7)
1st fasting day..........	48.1	25.5	17.7	14.5	7.6
2d " "	12.9	11.3	6.2	6.6	3.6
3d " "	7.1	4.7	5.5	3.7	2.9
4th " "	5.3	2.8	2.9	2.9	1.2
5th " "	0.3	0.6	2.2	2.8	0.7

The amount of extra protein metabolism is seen from the above to be directly dependent on the previous feeding, a common level being reached in all cases on the fifth day of fasting.

These experiments led Voit to differentiate between "circulating protein," which could be absorbed, carried to the tissues, and burned, and "organized protein," the more resistant living protein of the tissues themselves. Voit[1] stated that in metabolism the lifeless protein furnished to the cells by the blood was used in preference to the living organized tissue protein. He quoted Landois' experiments, which show that after producing an artificial plethora through injection of blood, the serum proteins are readily burned and their nitrogen eliminated in the urine, while the red blood-cells containing the organized protein are only slowly destroyed. If serum alone be transfused, its protein is rapidly destroyed.[2]

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[1] Voit: "Handbuch der Ernährung," 1881, p. 300.

[2] Forster: "Zeitschrift für Biologie," 1875, xi, 496.

Even in starvation there is evidence of "circulating protein" as food for the tissues. Thus Miescher showed that the salmon, after entering the Rhine from the sea, virtually starves. Yet the genital organs of both male and female develop greatly, this being at the expense of the muscles, which may lose 55 per cent. of their weight. This protein must have been carried to the various parts of the body in the circulating blood-stream. Miescher finds no indication of any destruction of muscle-fibers in this process of emaciation (see p. 249). It is interesting in this connection to note that A. R. Mandel[1] has been able at a pressure of 300 to 350 atmospheres acting on lean meat seventy-two hours old to press out a fluid containing 44 per cent. of the protein present in the fibers, and this without visible change from the normal histologic appearance of the muscle.

It seemed quite possible that in ordinary starvation protein from muscle and other tissues passed to the blood and was carried to all the organs as circulating protein for the nutrition of their cells.

The great work of Kossel, Hofmeister, and Emil Fischer has taught that the essential composition of protein is a structure formed of chains of amino-acids. Fischer has constructed artificial *peptids*, bodies in which two or more amino-acids are united together. For example, glycyl-glycin is formed by the union of two molecules of glycocoll with the loss of water, as follows:

$$\begin{array}{l} H_2NCH_2COOH \\ H_2NCH_2COOH \end{array} - H_2O = \begin{array}{l} H_2NCH_2CO \\ \quad | \\ \quad HNCH_2COOH \end{array}$$

Glycocoll. Glycyl-glycin.

Fischer has hung together eighteen of these radicles in an octodecapeptid containing four leucin and fourteen glycocoll molecules and being l-leucyl-triglycyl-l-leucyl-triglycyl-l-leucyl-octoglycyl-glycin.

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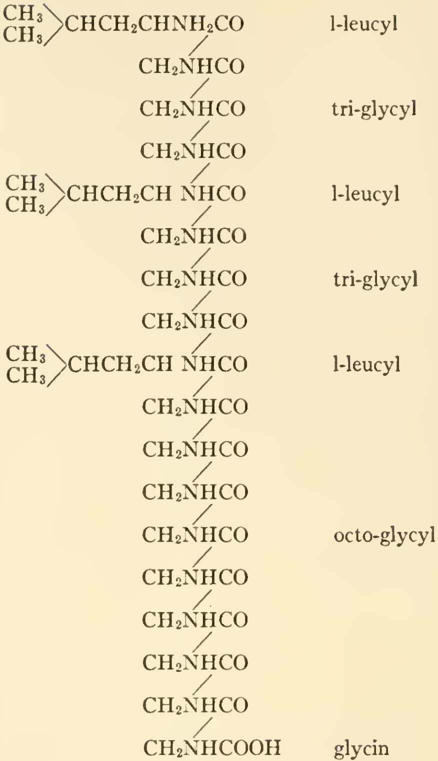
[1] Mandel: Unpublished work from the Munich Clinic of Prof. Fr. Müller.



N = 20.8 per cent.

This forms a body akin to pepton. The high molecular complexes called proteins, which constitute the basis of our being, are, after all, separable into simple chemical compounds. In the larger molecule these amino-acids are chained together, even as in structural framework various iron beams are riveted together. Digestive proteolysis or internal metabolism rends the higher structure of the molecule and leaves its individual supports, the amino-acids, open for further disintegration.[1]

The various proteins differ from one another in the relative quantity of the different amino-acids which they contain,

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[1] For further details see Plimmer: "The Chemical Constitution of the Proteins," 1908.

and also undoubtedly in the manner of chemical linkage of those acids. Thus Abderhalden has called attention to the fact that if the seventeen different chemical units be joined together in different ways, 350,000,000 times 1,000,000 different combinations are possible even though only a single representative of each unit is used. In this manner the amino-acids may form combinations the possible multiplicity of which recalls the number of words in the dictionary formed from the letters of the alphabet.

The following table presents analytic data showing the approximate amounts of the different amino-acids contained in well-known varieties of vegetable and animal proteins:

COMPARATIVE COMPOSITION OF PROTEINS[1]

Amino-acids.	Zein (Maize).	Gliadin (Wheat).	Casein (Milk).	Lactalbumin (Milk).	Edestin (Hemp Seed).	Ox Muscle.[2]
	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.
Glycocoll	....	....	....	....	3.80	4.0
Alanin	13.39	2.00	1.50	2.50	3.60	8.1
Valin	1.88	3.34	7.20	0.90	6.20	2.0
Leucin	19.55	6.62	9.35	19.40	14.50	14.3
Prolin	9.04	13.22	6.70	4.00	4.10	8.0
Phenylalanin	6.55	2.35	3.20	2.40	3.09	4.5
Aspartic acid	1.71	0.58	1.39	1.00	4.50	10.6
Glutaminic acid	26.17	43.66	15.55	10.10	18.74	22.3
Serin	1.02	0.13	0.50	?	0.33	?
Tyrosin	3.55	1.50	4.50	2.20	2.13	4.4
Cystin	?	0.45	?	?	1.00	?
Histidin	0.82	1.84	2.50	2.06	2.19	4.5
Arginin	1.55	2.84	3.81	3.23	14.17	11.5
Lysin	....	0.93	7.61	9.16	1.65	7.6
Tryptophan	....	1.00	1.50	+	+	+
Ammonia	3.64	5.22	1.61	1.32	2.28	1.07
	88.87	85.68	66.92	58.27	82.28	102.87

Concerning the crystalline vegetable proteins which he has investigated Osborne[3] writes: "It is possible to establish a

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[1] Osborne, T. B., and Mendel, L. B.: "Journal Biological Chemistry," 1914, xvii, 336, modified as to the arginin, histidin, and lysin content of gliadin and lactalbumin to accord with Osborne, Van Slyke, Leavenworth, and Vinograd, *Ibid.*, 1915, xxii, 259.

[2] Osborne and Jones: "American Journal Physiology," 1909, xxiv, 437, modified by the findings of Osborne and Jones, *Ibid.*, 1910, xxvi, 305.

[3] Osborne: "Science," 1908, xxviii, 417.

constancy of properties and ultimate composition between successive fractional precipitations which give no reason for believing the substance to be a mixture of two or more individuals. On chemical grounds there is no more reason for dividing the proteins into two groups of animal and vegetable proteins than there is in making a similar distinction between the carbohydrates. Of twenty-three seed proteins which have been hydrolized, all have yielded leucin, prolin, phenylalanin, aspartic acid, glutamic acid, tyrosin, histidin, arginin, and ammonia. Glycocoll, lysin, and tryptophan are the only amino-acids which have been proved lacking in any one of these proteins."

Osborne and Abderhalden are agreed that the chemical constituents of protein are probably all known, and that the usual deficit found on their analysis is due to the inadequacy of the methods employed. Thus Osborne and Jones found that they recovered varying percentages of different amino-acids when a mixture of known quantities was analyzed. If one computes their analysis of ox muscle protein on the basis of analytic losses similar to those found when the mixture of known quantities of amino-acids was analyzed, one obtains nearly 103 per cent. of the value of the original ox protein. This value includes the water added by hydrolysis in the break up of the molecule.

Osborne finds that the quantity of ammonia liberated in hydrolysis bears a constant relation to the amount of glutamic and aspartic acids recovered. He concludes that one of the carboxyl groups (COOH) exists as an amid $(CONH)_2$, and that in reality glutamin and asparagin are present in the molecule, and become the sources of ammonia when the molecule is broken.

The physiology of protein metabolism has become in late years the physiology of the amino-acids. When once so regarded, the problem is one of the study of the behavior within the body of chemical entities which can be prepared in pure crystalline form and the formulæ of which are definitely known. The fate of these individual amino-acids will be considered at another time (see p. 184). It is sufficient to state here that the cleavage of protein into amino-acids through digestion hydrolysis is accomplished without the liberation of an appreciable quantity of heat,[1] that the resulting amino-acids are absorbed directly into the bloodstream, and that in so far as they are reconstructed into new protein within the organism the process takes place without any measurable thermodynamic reaction (see p. 245). Since the protein content of blood-plasma is nearly the same in fasting as after large ingestion of meat, it is evident that the storage of such ingested protein must be effected elsewhere than in the blood.

A preliminary survey of the more recently discovered information regarding the interplay between the proteins and the amino-acids of the organism may be of service at this juncture. The absorption of amino-acids by the blood was first indicated by the work of Howell,[2] who dialyzed dog's blood both before and after giving meat, and in the latter instance recovered more material on adding naphthylsulphochlorid to the diffusate than in the former. The precipitate, however, was an oil and its quantity could not be measured accurately. Folin and Denis[3] introduced glycocoll or alanin into the small intestines of cats, and on analyzing the blood and muscle tissue noticed a large increase in the quantity of "residual nitrogen" which was obtained by subtracting "urea nitrogen" from "total non-protein nitrogen." The increase was so great that it could only have been caused by the influx of the amino-acids themselves. An hour after the introduction of the amino-acids urea appeared in increased quantity in the blood. Their results indicate that absorbed amino-acids circulate in the blood, are retained in the muscle tissue, and that after an hour urea rises in the blood in response to the

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[1] Hári: "Pflüger's Archiv," 1906, cxv, 11.

[2] Howell, W. H.: "American Journal of Physiology," 1906, xvii, 273.

[3] Folin and Denis: "Journal of Biological Chemistry," 1912, xii, 141, and previous papers.

increased production of urea in the tissues. They found no increase in the quantity of urea or of ammonia in the blood of the portal vein after introducing glycocoll or alanin into a loop of the intestine, and by this experiment demonstrated that the amino-acids were absorbed unchanged without deamination, which would have involved ammonia or urea production.

Van Slyke and Meyer[1] were able to determine directly amino-acids in the blood. Thus the absorption of 12 grams of glycocoll from the intestine of a dog caused an increase in the amino-acid content of the blood from 3.9 to 6.3 milligrams per 100 c.c. of blood volume. After giving 1000 grams of meat to a dog the amino-acid content of the blood doubled or more than doubled in a mesenteric vein, and the urea content also increased. There was almost as great an increase in the amino-acid content of the femoral vein as in the mesenteric, and therefore Van Slyke concludes that amino-acids are not largely retained by the liver.

Van Slyke and Meyer[2] have confirmed the work of Folin and Denis in showing that the tissues absorb amino-acids with great avidity. The normal concentration of amino-acids in the tissues were found to be five to ten times that in the blood. Optimal figures are given as 80 milligrams per 100 grams of muscle, and 150 milligrams per 100 grams of liver. In one experiment the introduction into the vein of a dog of amino-acids derived from casein and containing 4.06 grams of nitrogen resulted after half an hour in an increase of amino-acids in the blood from 3.9 to 45.4 milligrams per 100 grams. This quantity would account for 5 per cent. of the total amount injected, and since 11 per cent. was eliminated in the urine it appears that the remainder or 3.41 grams of N must have been absorbed by the tissues.

Finally, it was shown by Van Slyke and Meyer[3] and independently by Wishart[4] that although the ingestion of meat

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[1] Van Slyke and Meyer: "Journal of Biological Chemistry," 1912, xii, 399.

[2] *Ibid.*, 1913–14, xvi, 197.

[3] *Ibid.*, 1913–14, xvi, 231.

[4] Wishart: "Journal of Biological Chemistry," 1915, xx, 535.

in large quantity increases the amino-acid content of the blood, it does not increase that of muscle tissue. It is therefore probable that when nitrogen is retained in the organism it is not to an appreciable extent stored as digestion products, but rather in the form of protein (see p. 169). Such amino-acids as are not so synthesized are, therefore, destroyed as rapidly as they accumulate.

Van Slyke and Meyer[1] conclude that absorbed amino-acids disappear rapidly from the liver, although their concentration in the muscle suffers no appreciable fall. The urea concentration in the blood increases. The liver desaturates itself and in this way metabolizes superfluous protein.

On the other hand, Fiske and Sumner,[2] in Folin's laboratory, after tying a ligature around the portal vein and hepatic artery of a dog, find that intravenous injection of amino-acids leads to as great a formation of urea as in a normal animal. They explain Van Slyke's results as indicating that the liver might rid itself of amino-acids as it does of glycogen without being of necessity involved in their destruction.

In this relation it may be added that Abderhalden[3] showed several years ago that tryptophan was converted into kynurenic acid as readily in a dog with an Eck fistula (see p. 451) as in one without.

The first actual isolation of an amino-acid from blood was reported by Abel[4] at the International Physiological Congress held at Groningen in the summer of 1913. Alanin was found in considerable amount in a diffusate formed by dialyzing the blood during its continuous passage from an artery of a living animal through a system of tubes made of

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[1] Van Slyke and Meyer: "Journal of Biological Chemistry," 1913–14, xvi, 213.

[2] Fiske and Sumner: "Journal of Biological Chemistry," 1914, xviii, 285.

[3] Abderhalden, London, and Pincussohn: "Zeitschrift für physiologische Chemie," 1909, lxii, 139. Consult also Mathews and Nelson: "Journal of Biological Chemistry," 1914, xix, 229; Taylor and Lewis: *Ibid.*, 1915, xxii, 77.

[4] Abel, Rowntree, and Turner: "Journal of Pharmacology and Experimental Therapeutics," 1913–14, v, 611.

celloidin immersed in a saline solution, the blood then returning to the animal by a vein. This method of *vividiffusion* yields alanin in crystalline form. Histidin and creatinin may be determined by color reactions. Sugar, urea, ammonia β-oxybutyric acid, and lactic acid also diffuse from the blood in marked amounts.

Abderhalden[1] worked with 50 and 100 liters of blood-serum and reports the presence of ten different amino-acids. Abel[2] calls attention to the fact that secondary changes which may conceivably take place in shed and coagulated blood play no part in his method of vividiffusion, which separates diffusible substances from the circulating blood of living animals.

Van Slyke and Meyer[3] report that free amino-acids do not disappear from the tissues on fasting, but, if anything, they tend to increase there.

These facts are interpretative of conditions in fasting. That amino-acids are produced in fasting is demonstrated in the cited instance of the salmon in which the protein of the genital organs increases at the expense of muscle protein. Thus Kossel[4] estimates that a salmon weighing 9 kilograms deposits at breeding time in its testicles 27 grams of salmin containing 22.8 grams of arginin. Kossel calculates that metabolism of muscle protein during this time yields ample arginin to form the new salmin.

Other evidence of the constant production of amino-acids in the tissues in fasting is offered by the experiments of Turner, Marshall, and Lamson.[5] In these important investigations one-third the blood of a dog was withdrawn, the blood corpuscles were washed with normal saline, and then the washed corpuscles were returned to the body. This process is called

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[1] Abderhalden: "Zeitschrift f. physiolog. Chem.," 1913, lxxxviii, 478.

[2] Abel: First Mellon Lecture, University of Pittsburgh, 1915, p. 22.

[3] Van Slyke and Meyer: "Journal of Biological Chemistry," 1913-14, xvi, 231.

[4] Kossel: "Biochemisches Zentralblatt," 1906, v, 33.

[5] Turner, Marshall and Lamson: "Journal of Pharmacology and Experimental Therapeutics," 1915, vii, 129.

by Abel *plasmapharesis*. Three such bleedings, with the return of the corpuscles in a volume of saline solution equal to that of the serum removed, should theoretically reduce the serum protein to 30 per cent. of that originally present, provided there were no renewal of the plasma protein. But there is a fairly rapid flow of protein into the plasma from supplies existing in other tissues, so that the serum protein after three successive bleedings amounts to about 50 per cent. of the quantity ordinarily present. Notwithstanding the fall in protein in the blood-plasma, the quantity of urea increases and the amino-acid nitrogen remains constant. These relations are shown in the following table which compares the analysis of the normal blood and that obtained after five days of plasmapharesis, during which time one-third of the blood was withdrawn fifteen times, a total amount of bleeding equal to more than fivefold the quantity of blood in the fasting animal.

EFFECT OF PLASMAPHARESIS UPON THE COMPOSITION OF DOG'S BLOOD

	Total Protein.	Plasma Protein.	Blood-count.	Urea N.	Amino N.
	Per cent.	Per cent.	Millions.	Per cent.	Per cent.
Original blood..........	19.28	6.38	8.50	0.013	0.0047
After five days of plasmapharesis ..	15.83	2.92	6.50	0.021	0.0059

The reaction of the organism which causes an increase in the amount of its protein metabolism after reducing the amount of serum protein is also shown in the experiments of Taylor and Lewis,[1] who withdrew blood repeatedly at hourly intervals and substituted saline for it in a dog. In this manner the quantity of serum proteins was reduced to only 2.7 per cent., although the quantity of amino-acid nitrogen and of urea increased in the serum.

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[1] Taylor and Lewis: "Journal of Biological Chemistry," 1915, xxii, 72.

These facts accord with the older work of Bauer[1] in Voit's laboratory, who found an increased nitrogen elimination in the urine following bloodletting.

Summarizing this discussion, it becomes clear that though the body is built up of proteins which are aggregates of amino-acids, these same amino-acids occur free in only minimal amounts, 4 parts in 100,000 in blood, for example, and 40 to 80 parts in 100,000 in muscle. These small amounts are constantly present and apparently are the precursors of urea. After giving meat in large quantity the amino-acid concentration rises in the blood, but not in the tissues, for in the tissues the amino-acids are either destroyed with the production of urea or they are reconstructed into body protein, thus becoming "deposit protein" (see p. 286). When starvation takes place it is obvious that the quantity of protein destroyed may depend upon the protein condition of the cells themselves, and that in the presence of much "deposit protein" this may be metabolized in large quantity during the first few days, as is indicated by a high nitrogen elimination in the urine.

This principle appears not only in the dog, as before stated, but also in man. This is shown in the experiments of Karl Thomas (see p. 275), narrated by Rubner,[2] although in this work carbohydrates were ingested. The daily diet of a man contained 89 grams of protein nitrogen or 4.5 per cent. of the total protein nitrogen content of his organism. During the last day of this diet the man eliminated 77.7 grams of nitrogen in the urine. Then the man was given a diet of starch and sugar, both of which were free from protein, and the nitrogen elimination in the urines of successive days was determined as follows: 28.3; 10.7; 5.15; 5.16; 4.72; 3.93; 3.46; nine-day interval: 3.06; 2.31; 2.16. The gradual elimination of "deposit protein" with the tendency of the total protein metabolism to fall to lower and lower levels is, therefore, a

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[1] Bauer: "Zeitschrift für Biologie," 1872, viii, 567.
[2] Rubner: "Archiv für Physiologie," 1911, p. 61.

concomitant of protein starvation. It seems that it is this gradual metabolism of "deposit protein," in addition to the constant and necessary metabolism of the protein built into living substance of the cells, which determines the higher level of the protein metabolism during the early days of fasting.

During true fasting it is quite possible that the full extent of protein metabolism is not measured by the nitrogen in the urine, for it may be that muscle proteins are converted into amino-acids which are transported to other organs, to the heart, for example, for the replenishment of an organ which scarcely loses weight during the ordeal of life without food. Such a procedure would be akin to the development of the genital organs of the salmon already described.

It will be perceived that although Voit's term "circulating protein" is, generally speaking, a misnomer, yet it served the useful purpose of sharply differentiating the more resistant behavior of living tissue protein from that of ingested protein, and from the material now known as "deposit protein," ingested protein being very readily, and deposit protein quite readily, metabolized.

This point is furthermore well illustrated by the behavior of gelatin. Voit has demonstrated that although gelatin can never be converted into tissue protein nor retained in the body, its ingestion may in part prevent the combustion of the living protein tissue of the body (see page 156).

The amount of protein metabolized by a starving animal in good condition bears a constant relationship to the total metabolism involved. Even in different animals this constancy is observed. E. Voit[1] calls attention to the fact that the nitrogen elimination is not dependent on the weight of the animal, since a pig of 115 kilos produces 0.06 gram per kilo, whereas a guinea-pig weighing but 0.6 kilo eliminates 0.65 gram of nitrogen per kilo, or ten times as much. However, a comparison of the percentage of the total energy derived from

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[1] E. Voit: "Zeitschrift für Biologie," 1901, xli, 188.

protein in fasting animals in good condition (*i. e.*, with considerable fat) varies within much narrower limits—between 7.3 and 16.5 per cent. This is shown in the following table:

NITROGEN METABOLISM OF DIFFERENT ANIMALS IN STARVATION.

Animal.	Weight in Kg.	N Elimination.			Percentage of Calories from Protein.
		Total.	Per Kg.	Per Sq. M. Surface.	
Pig	115.0	6.8	0.06	3.2	7.3
Man	63.7	12.6	0.20	6.4	15.6
Dog I	28.6	5.1	0.18	5.2	13.2
Dog II	18.7	3.8	0.20	4.6	10.7
Dog III	7.2	2.2	0.30	5.2	13.5
Rabbit	2.7	1.2	0.46	4.8	16.5
Goose	3.3	0.8	0.23	3.3	7.4
Fowl	2.1	0.7	0.34	4.2	10.0
Guinea-pig	0.6	0.4	0.65	4.2	10.8

It is evident from the above that an average of 90 per cent. of the energy of the fasting metabolism may be supplied by non-protein material. This material is fat (see page 27).

If a fasting organism be kept at the same temperature and under the same conditions as regards the performance of external work, the metabolism is remarkably even from day to day.

Hanriot and Richet[1] showed the even absorption of oxygen and elimination of carbon dioxid during the early days of fasting in man, as is illustrated in this table:

	Liters O_2 per Hour.	Liters CO_2 per Hour.
After 17 hours' fast	17.4	15.3
" 24 " "	16.85	14.15
" 29 " "	16.05	14.3
" 46 " "	16.9	14.35

Later Lehmann and Zuntz[2] made some experiments on the professional faster Cetti. They analyzed his urine and feces, and also obtained two samples of the carbon dioxid eliminated

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[1] Hanriot and Richet: "Comptes rendus de l'Académie des Sciences," 1888, cvi, 496.

[2] Lehmann and Zuntz: "Arch f. pathol. Anat.," 1893, cxxxi, Suppl., 23.

between 10 and 11 A. M., each period of collection lasting from ten to fourteen minutes. In other words, the carbon dioxid output was determined for only twenty to twenty-six minutes daily. From these data the total day's metabolism was calculated. This apparatus as used by Zuntz has the advantage that it can be made in portable form, and may be carried on the back in mountaineering. The person inspires through a mouth-piece provided with a plate of hard rubber which fits between the lips and the teeth. The nostrils are closed with a clamp. The inspired air is drawn through a valve and the expired air is forced through another valve to a gas-meter. Arrangements are also provided for the gas analysis of portions of the expired air. Trustworthy results are obtained only when the person under investigation is accustomed to the apparatus. It is of especial value when pronounced temporary variations in the metabolism are to be measured.

The record of the metabolism of Cetti during a ten days' fast was as follows:

METABOLISM OF CETTI IN STARVATION

Fasting Days.	Protein.	Fat.	Calories from Protein.	Calories from Fat.	Calories, Total.	Calories per Kilo.
1 to 4......	85.88	136.72	329.8	1288.2	1618	29.00
5 to 6......	69.58	131.30	267.3	1237.4	1504	28.38
7 to 8......	66.30	149.35	254.7	1407.3	1662	31.74
9 to 10......	67.96	132.38	261.1	1247.4	1508	29.26

A very careful experiment on the metabolism of a fasting medical student twenty-six years old was made by Johansson, Landergren, Sondén, and Tigerstedt.[1] The man fasted five days, doing light work in the respiration apparatus. The metabolism during these days was determined. The excreta in grams were as follows:

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[1] Landergren, Sondén, and Tigerstedt: "Skandin. Archiv für Physiologie," 1897, vii, 54.

METABOLISM OF J. A. IN STARVATION

Day of Fasting.	N Elimination.			C Elimination.			
	Urine.	Feces.	Total.	Urine.	Feces.	Respiration.	Total.
1	12.04	0.13	12.17	8.0	1.1	188.5	197.6
2	12.72	0.13	12.84	8.3	1.1	179.4	188.8
3	13.48	0.13	13.61	9.9	1.1	172.2	183.2
4	13.56	0.13	13.69	10.3	1.1	169.4	180.8
5	11.34	0.13	11.47	9.3	1.1	165.8	176.2

The evenness of the carbon and nitrogen elimination is remarkable. From the above figures the following table of the general metabolism is made:

Day of Fasting.	Protein.	Fat.	Calories from Protein.	Calories from Fat.	Calories, Total.
1	76.1	206.1	303.5	1916.9	2220.4
2	80.3	191.6	320.5	1781.9	2102.4
3	85.1	181.2	339.4	1684.7	2024.1
4	85.6	177.6	341.4	1651.9	1992.3
5	71.7	181.2	286.1	1684.7	1970.8

Further calculation shows the following relations between the weight of the individual and the calorific production:

Day of Fasting.	Weight in Kilos.	Calories per Kilo.
1	66.99	33.15
2	65.71	32.00
3	64.88	31.20
4	63.99	31.13
5	63.13	31.23

On the fifth day of fasting it is seen that the individual oxidized 71.7 grams of protein, 181.2 grams of fat, and produced 1971 calories, or 31.23 calories per kilogram of body substance. This is presumably the minimum compatible with ordinary life.

Reference has already been made to the notable work of Benedict (p. 72), "The Influence of Inanition on "Metabolism."

Here in seventeen experiments on seven men the metabolism was determined during a fast of two days, and in one instance the starvation period extended over seven days. In these experiments the metabolism of glycogen was for the first time determined. Benedict's fasting individuals were placed in a respiration calorimeter, and in addition to the usual routine the amount of oxygen consumed by them was measured. Knowing the last factor, Benedict was able to calculate the amount of glycogen destroyed by deducting from the total oxygen intake the part necessary to oxidize the protein catabolized, and then, in the light of the knowledge of the respiratory quotient, apportioning the remainder of the oxygen to the non-protein carbon dioxid eliminated in such a way as to indicate the amounts of glycogen and fat destroyed (see p. 60). The heat value of the metabolism thus calculated agreed within ½ of 1 per cent. with the heat as actually measured by the calorimeter in which the man lived, whereas if the non-protein carbon of the first day had been reckoned as fat metabolized, as had heretofore been the custom, the discrepancy would have been as high as 5 per cent. in some instances. This shows the usefulness of a comparison of direct and indirect calorimetry (see p. 57).

The results of Benedict's experiment on an individual who fasted for seven days are here reproduced:

METABOLISM OF S. A. B. DURING A SEVEN-DAY FAST.

Day.	Grams.			Calories.				R. Q.	Urine.	
	Protein.	Fat.	Glycogen.	Calculated from Metab.	Directly Determined.	Per Kg.	Per Sq. M.		Ratio N : S.	Ratio $N:P_2O_5$.
1....	73.4	126.4	64.9	1796	1765	29.7	941	.78	19.6	8.55
2....	74.7	147.5	23.1	1790	1768	29.9	946	.75	18.6	5.55
3....	78.1	153.0	5.4	1785	1797	30.8	969	.74	17.38	6.34
4....	69.8	144.7	25.2	1734	1775	30.8	966	.75	16.11	4.83
5....	65.2	144.7	8.2	1636	1649	29.0	905	.74	16.26	5.23
6....	64.4	129.8	21.7	1547	1553	27.5	856	.75	16.27	5.19
7....	60.8	132.5	18.7	1546	1568	28.0	869	.74	16.28	4.87

This complete and recent experiment reaffirms the principles which have already been enunciated. Benedict found that the pulse-rate showed a distinct tendency to fall. In the above individual the average pulse-rate was 57 on the first fasting day and 51 on the seventh day.

E. Voit[1] gives the following summary of the energy requirements during the early days of starvation in man:

GENERAL TABLE OF STARVATION METABOLISM IN MAN

Day of Fast.	Weight.	Energy in Calories.			Author.
		Total.	Per Kg.	Per Sq. M. Surface.	
1........	70.6	2359	33.4	1112	Pettenkofer and Voit.
1........	70.4	2222	31.6	1060	Pettenkofer and Voit.
1 to 5....	64.9	2071	31.9	1042	Tigerstedt.
1........	59.5	1893	31.8	1012	Zuntz and Lehmann.
1 to 2....	56.0	1773	31.7	985	Zuntz and Lehmann.

To this may be added the average results of the many experiments by Benedict:

METABOLISM IN THE EARLY DAYS OF STARVATION

	1st Day.	2d Day.	3d Day.	4th Day.	5th Day.
No. of experiments...........	18	17	9	5	2
Average calories per kg........	30.7	31.8	31.0	29.6	28.5
Average calories per square meter surface (Meeh)..	992	1028	991	938	885

This minimal metabolism requirement of the fasting organism appears remarkably constant in different men. Not only is the total metabolism the same, but also the amounts of protein and fat which yield the energy are the same. This is shown by comparing the nitrogen excretion of the different fasters during the first days of fasting. These are as follows:

	Cetti.[2]	Breithaupt.[3]	Succi.[4]	J. A.[6]	Succi.[6]
1.................	13.55	10.01	13.81	12.17	17.00
2.................	12.59	9.92	11.03	12.85	11.20
3.................	13.12	13.29	13.86	13.61	10.55
4.................	12.39	12.78	12.80	13.69	10.80
5.................	10.70	10.95	12.84	11.47	11.19
6.................	10.10	9.88	10.12	.....	11.01

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[1] Voit, E.: "Zeitschrift für Biologie," 1901, xli, 114.

[2] Munk: "Arch. f. Path. Anat.," 1893, cxxxi, Suppl. 25.

[3] Munk: *Ibid.*, p. 68.

[4] Luciani: "Das Hungern," 1890.

[5] Johansson, Landergren, Sondén, and Tigerstedt: "Skandin. Archiv. für Physiol.," 1897, vii, 54.

[6] Freund, E. and O.: "Wiener klinische Rundschau," 1901, xv, 91.

It is thus evident that if the organism has previously been well nourished, the fasting metabolism is remarkably even, about 13 per cent. of the total energy being derived from protein and 87 per cent. from fat.

During prolonged fasting the nitrogen output sinks much below the figures of the earlier days. Thus a woman twenty-four years old averaged 4.15 gm. from the thirteenth to the twenty-fifth day of fasting.[1] A girl nineteen years old whose esophagus had been occluded by drinking sulphuric acid excreted 2.8 grams of nitrogen on the sixteenth day of fasting.[2] An invalid of Tuczec's[3] averaged 4.25 grams of nitrogen between the fifteenth and twenty-first days. Under Luciani's observation Succi excreted 4.08 grams on the twenty-ninth day, and under E. and O. Freund his nitrogen excretion was 2.82 grams on the twenty-first day. The latter authors say that after this there was a sudden rise in the amount of nitrogen and chlorin in the urine, suggesting the so-called *premortal rise*, which caused them to stop the experiment. About 3 grams of nitrogen in the urine or a daily destruction of 18.75 grams of protein would seem to be the lowest extreme of protein metabolism in the emaciated organism after a prolonged fast. The analyses by E. and O. Freund of Succi's urine during a fast of twenty-one days was the first complete record of the sort. The daily nitrogen excretion is given in grams below:

DAILY NITROGEN EXCRETION OF SUCCI IN STARVATION

Day.	N.	Day.	N.	Day.	N.
1	17.0	8	9.74	15	5.05
2	11.2	9	10.05	16	4.32
3	10.55	10	7.12	17	5.4
4	10.8	11	6.23	18	3.6
5	11.19	12	6.84	19	5.7
6	11.01	13	5.14	20	3.3
7	8.79	14	4.66	21	2.82

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[1] Seegen: "Wiener Acad. Sitz. Ber.," Bd. xxxiii, 2 Abth.

[2] Schultzen: "Archiv für Anatomie und Physiologie," 1863, p. 31.

[3] Tuczec: "Arch. für Psychiatrie," 1884, xv, 784.

The nitrogen and total sulphur ran together in the urine in the proportion of 17.3 N : 1 S. Munk found the ratio $\frac{N}{S}$ to be 14.7 in Breithaupt and 15.1 in Cetti, and Benedict (see p. 89) found 16.27 during the fifth, sixth, and seventh days of starvation. A similar relation between N and S is found in muscle. The sulphur is believed to be derived exclusively from the breaking down of protein.

The nitrogen and total phosphoric acid (P_2O_5) in the urine are not found in the same ratio as that in which they exist in meat (7.6 : 1), but there is a greater phosphoric acid excretion. This is also true of the calcium excretion. This greater excretion is due to the metabolism of the bones (Munk). E. and O. Freund found that the $\frac{N}{P_2O_5}$ fell from 5.7 on the first day of Succi's starvation to between 4.2 and 4.4 during the subsequent periods. Munk found this value to be 4.4 in Cetti during ten days and 5.1 in Breithaupt during six days (consult table on p. 96).

Albumin is of frequent occurrence in the starvation urine of man and animals.

URINARY ANALYSIS OF VICTOR BEAUTE ON THE FIRST, THIRD, TWELFTH, AND FOURTEENTH DAYS OF FASTING.

WEIGHT IN GRAMS.

	Day of Fasting.			
	1st.	3d.	12th.	14th.
Total N	10.51	13.72	8.77	7.78
Urea N	8.96	12.26	6.62	5.99
Ammonia N	0.40	0.73	1.05	0.73
Uric acid N	0.12	0.06	0.17	0.17
Purin base N	0.029	0.032	0.023	
Creatinin N	0.42	0.34	0.30	0.24
Creatin N	0.02	0.09	0.09	0.10
Total S	0.614	0.801	0.577	0.536
Total P_2O_5	2.26	2.98	1.55	1.25
Cl	3.2	1.5	0.18	0.24
Ca	....	0.216	....	0.096
Mg	....	0.131	....	0.037
K	....	1.33	....	0.515
Na	....	0.865	....	0.096

A modern chronicle of the urinary excretion during fasting is presented in an experiment by Cathcart[1] on a professional faster, thirty-one years old, a part of which is reproduced on p. 92.

In this experiment the ammonia excretion rose to meet an accompanying acidosis. The creatinin excretion gradually fell, whereas the creatin excretion (see p. 211) remained quite constant. The ratio between the nitrogen and sulphur elimination averaged 15 N : 1 S, or similar to the relation found in muscle, which is 14 N : 1 S. The relatively large potassium excretion and the small sodium excretion indicated respectively the destruction of body tissues which are all rich in potassium salts and the conservation of the body's sodium chlorid supply.

A communication by Brugsch[2] shows that the quantities of β-oxybutyric acid and acetone in the urine become very great in extreme hunger. The experiment was also on Succi, between the twenty-third and the thirtieth days of starvation, and showed the following remarkable values:

ACETONURIA IN STARVATION (SUCCI)

Starvation Day.	N in Grams.	β-oxybutyric Acid in Grams.	Acetone in Grams.
23d	5.87	9.24	0.569
24th	6.41	8.43	0.410
25th	6.27	9.85	0.463
26th	6.18	5.28	0.569
27th	6.30	11.62	0.525
28th	4.43	6.99	0.339
29th	4.19	9.15	0.242
30th	8.42	13.60	0.115

The excretion of urea nitrogen ran between 54 and 70 per cent., and the ammonia nitrogen between 15.4 and 35.3 per cent. of the total nitrogen in the urine. The high ammonia neutralized the very considerable acidosis.

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[1] Cathcart: "Biochemische Zeitschrift," 1907, vi, 109.

[2] Brugsch: "Zeitschrift für ex. Pathologie und Therapie," 1905, i, 419.

Grafe[1] reports the excretion of 16.25 and 15.41 grams of urinary acetone bodies during the sixteenth and eighteenth days of fasting in a stuporous patient suffering from katatonic rigidity and lying in deep sleep on these days.

Folin and Denis[2] have described results concerning the development of acidosis in two obese women, patients of Dr. J. H. Means.[3] Mrs. M., weighing 108 kilograms, whose height was 149.7 cm. (4 ft. 1 in.), underwent 3 different periods of fasting, with the following results:

ACIDOSIS IN OBESITY

No. of Fast.	Day of Fast.	Urine N.	β-oxy-butyric Acid.	NH₃.	Acidity N/10 Alkali.
		Grams.	Grams.	Grams.	C.c.
I..........	4	9.4	18.47	2.50	695
II..........	5	5.2	13.54	1.50	655
III..........	4	4.5	17.34	0.81	300

Headache and nausea were present on these fourth and fifth days of fasting, symptoms which disappeared as if by magic after the patient took one piece of toast and a cup of tea. The authors state, "If the preceding subject was fat, our next one, Mrs. B., was a veritable pork barrel." Mrs. B. weighed 178 kilograms and measured 163.5 cm. (5 ft., 4½ in.) in height. She did not show the same intensity of acidosis manifested by the other patient, the largest quantity of β-oxybutyric acid eliminated reaching only 7.2 grams on the seventh day of a third fasting period. From these results it was concluded that obesity itself was not a predisposing cause of acidosis. In general, it was observed that the protein metabolism was low in these persons in whom ample fat was present (see p. 100), that repeating the fast lowered the protein metabolism (see Hawk, p. 104), and also that repeated fastings habituated the organism to the complete oxidation of fats as evidenced by a decrease in the amount of β-oxybutyric acid eliminated on

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[1] Grafe: "Zeitschrift für physiologische Chemie," 1910, lxv, 21.
[2] Folin and Denis: "Journal of Biological Chemistry," 1915, xxi, 183.
[3] Means: "Journal of Medical Research," 1915, xxxii, 121.

corresponding days of the several fasts. In this connection the observation of Abderhalden and Lampé,[1] that fasting progressively increases the power of dog's blood to split tributyrin, is of significance in showing adaptative power by the organism. Folin and Denis conclude that the method of repeated fasting applied to the obese is safe, harmless, and effective, provided the intensity of the acidosis be carefully followed.

In a way the results here mentioned are all summarized in the extended work of Benedict[2] upon a subject L., who fasted for thirty-one days. Benedict found no evidence of any disturbance of the higher mental functions of the subject. He found a lowered power of endurance during the fast, but, according to tests made a year later, could discover no lasting evil effect of the fast either upon muscular strength or mental activity. It is recorded that no feces were passed during the entire fast.

The chart (page 96) illustrates the principal data and a table (page 97) is also given which shows the most important determinations made on the first, eleventh, twenty-first, and thirty-first days of fasting.

The lowest average heat production of the fasting subject when in the bed calorimeter during the night was on the thirtieth day, and amounted to 1025 calories calculated for a twenty-four-hour period, or 661 calories per square meter of surface (Du Bois Height-weight Formula).

During the fast the man lost 277 grams of nitrogen from his body. If one may estimate with Rubner that a man under conditions of normal nutrition contains 30 grams of nitrogen per kilogram of body weight, then the original nitrogen content of the subject was 1788 grams. A loss of 277 grams would represent 16 per cent. This loss occurred during a period when the heat production fell from 1441 to 1025

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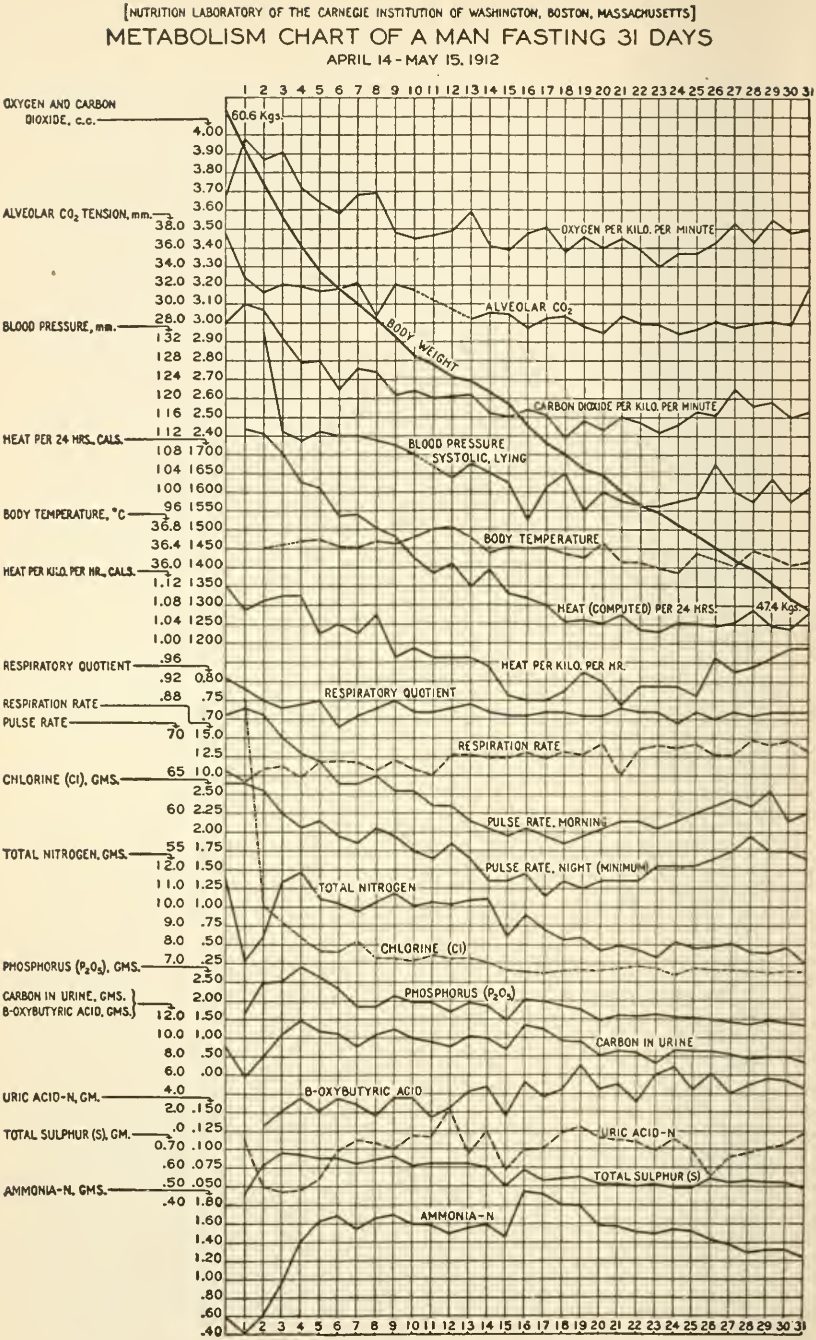
[1] Abderhalden and Lampé: "Zeitschrift für physiologische Chemie," 1912, lxxviii, 398.

[2] Benedict, F. G.: "A Study of Prolonged Fasting," Carnegie Institution of Washington, 1915, Publication 203.


[NUTRITION LABORATORY OF THE CARNEGIE INSTITUTION OF WASHINGTON, BOSTON, MASSACHUSETTS]

METABOLISM CHART OF A MAN FASTING 31 DAYS

APRIL 14 - MAY 15, 1912

Fig. 4.

SUBJECT L. HEIGHT, 170.7 CM. ONLY DISTILLED WATER WAS TAKEN DURING THIS FAST

	Day of Fasting.			
	1st	11th	21st	31st
Body weight, kg	59.60	53.88	50.49	47.39
Rectal temperature at 7 A. M.	....	36.54	36.04	35.96
Pulse-rate, morning, awake	74	61	59	60
Hemoglobin in per cent	90	85	88	92
Alveolar CO_2 tension (Haldane)	32.8	....	28.7	31.8*
Urine: Total solids	43.51	42.05	31.88	27.07
Total N	7.10	10.25	7.93	6.94
Urea N	5.68	7.66	5.54	4.84
Ammonia N	0.41	1.58	1.57	1.24
Uric acid N	0.112	0.116	0.112	0.122
Creatinin + Creatin N	0.48	0.49	0.38	0.32
Chlorin	3.77	0.36	0.18	0.13
P_2O_5	1.66	1.95	1.60	1.32
N : P_2O_5	4.28	5.26	4.96	5.26
S	0.46	0.62	0.51	0.49
N : S	15.4	16.5	15.5	14.2
β-oxybutyric acid	....	1.4	5.0	4.5
Ca	0.217	0.220	0.237	0.138
Mg	0.046	0.072	0.053	0.052
K	1.630	1.006	0.644	0.606
Na	2.070	0.100	0.066	0.053
C : N	0.820	0.936	1.083	1.062
Calories N	9.15	10.73	11.98	11.53
Loss of flesh calculated from N loss	213	308	238	208
CO_2, night, c.c. per minute	165	128	112	115
O_2, night, c.c. per minute	212	176	154	160
R. Q., night	0.78	0.72	0.73	0.72
H_2O per hour	22.8	18.3	14.6	17.9
Per cent. of calories from protein	10.6	19.6	16.5	14.4
Calories, indirect, twenty-four hours' complete rest	1441	1193	1032	1072†
Calories per square meter (DuBois), twenty-four hours	843	732	653	701‡
Calories per kilogram, twenty-four hours	24.2	22.1	20.4	22.6

* Previous day = 27.8. † Previous day = 1025. ‡ Previous day = 661

calories, a reduction of 29 per cent. It is, therefore, evident that the fall in metabolism reaches greater proportions than does the fall in the mass of protoplasmic tissue.

There seems to be a specific reduction in metabolism coincident with undernutrition (see p. 476). Unfortunately, when food was taken after the fast digestive disturbances marred the records of this subject. It would have been interesting to ascertain whether his metabolism on the second or third day of food ingestion was normal according to the unit of surface.

Benedict calls attention to the fact that there is a parallelism between the amounts of magnesium and of nitrogen eliminated in the urine.

The following analysis of the derivation of the source of the mineral constituents in the urine of Benedict's subject L. may be made. Katz[1] reports upon the quantities of the mineral constituents of human flesh, as obtained from a suicide on the day of death:

MINERAL ANALYSIS OF FRESH HUMAN MUSCLE

Parts in 1000

K.	Na.	Fe.	Ca.	Mg.	P_2O_5.	Cl.	S.
3.20	0.80	0.15	0.075	0.212	4.68	0.70	2.08

On this basis a calculation has been made of the mineral content of the "flesh" computed to have been destroyed on three different days in the fasting subject L., and these calculated values have been compared with the minerals actually excreted in the urines of these days. The following table presents these details:

SUBJECT L. ESTIMATED SALT SUPPLY FROM "FLESH" METABOLIZED ON THE ASSUMPTION THAT THIS WAS MUSCLE TISSUE, COMPARED WITH THE LOSS OF SALTS IN THE URINE

	Day of Fast.	K.	Na.	Ca.	Mg.	P_2O_5.	Cl.	S.
In 308 g. flesh	11	0.986	0.246	0.023	0.065	1.44	0.22	0.64
In urine		1.006	0.100	0.220	0.072	1.95	0.36	0.62
Difference		−0.020	+0.146	−0.197	−0.007	−0.51	−0.14	+0.02
In 238 g. flesh	22	0.762	0.190	0.018	0.050	1.11	0.17	0.50
In urine		0.643	0.066	0.237	0.053	1.60	0.18	0.51
Difference		+0.119	+0.124	−0.219	−0.003	−0.49	−0.01	−0.01
In 208 g. flesh	31	0.665	0.166	0.016	0.044	0.97	0.15	0.43
In urine		0.606	0.053	0.138	0.052	1.32	0.13	0.49
Difference		+0.059	+0.113	−0.122	−0.008	−0.35	+0.02	−0.06

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[1] Katz: "Pflüger's Archiv," 1896, lxiii, 1.

It is apparent that the quantities of potassium, magnesium, and sulphur eliminated in the urine are essentially those which might have been derived from the tissue destroyed. Sodium is constantly retained by the organism, whereas the loss of calcium and P_2O_5 represents osseous destruction. Since bones contain 24.48 per cent. of calcium and only 0.1 per cent. of magnesium, the loss of magnesium from this source would not be appreciable.

It seems clearly evident that the urinary waste of mineral constituents is largely composed of metabolized muscle or tissue analogous in composition to muscle, and of metabolized bone tissue.

It has already been set forth that the general metabolism is extremely even in fasting, and it may be added that existing evidence shows that the intermediary metabolism has a similar character. Thus Stiles and Lusk[1] found in a fasting dog made diabetic with phlorhizin that whereas the quantity of nitrogen and sugar eliminated slowly fell, the ratio between the two (the Dextrose : Nitrogen or D : N ratio) remained constant. This is shown in the following table:

CONSTANT RATIO BETWEEN DEXTROSE PRODUCTION AND N ELIMINATION IN STARVATION

Period.	D per Hour.	N per Hour.	D : N.
15 hours	2.61	0.735	3.56
6 "	....	0.720	
3 "	....	0.683	
12 "	2.39	0.666	3.60
3 "	2.51	0.687	3.65
6 "	....	0.670	
3 "	2.36	0.643	3.66
11 "	2.32	0.642	3.62

The hour-to-hour sugar production from protein is therefore even and constantly proportional to the protein metabolism.

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[1] Stiles and Lusk: "American Journal of Physiology," 1903, x, 77.

The length of life under the condition of starvation generally depends upon the quantity of fat present in the organism at the start. The quantity of fat and protein in an animal at the beginning of starvation or at any time during starvation may be estimated if the day-to-day metabolism be determined and if the whole animal be analyzed for fat and protein at the time of death. The sum of the quantities remaining in the body, and the quantity of waste of previous days, will give the composition of the animal at any definite date during the experiment. E. Voit[1] shows that a rabbit with an original fat content of 7 per cent. lived nineteen days and lost 49 per cent. of his body protein. Another rabbit with an original fat content of only 2.3 per cent. lived but nine days, while the loss of body protein amounted to 35 per cent. At the death of these rabbits the amount of fat found was very small, and the general vitality toward the end was almost exclusively maintained by the combustion of protein. Other animals, however, which lost 22 to 26 per cent. of their protein contained considerable fat at the time of death (see table, p. 103). E. Voit finds that the greater the amount of fat in the body, the less is the protein metabolism. In animals of equal fat content the relation between the amount of fat and the amount of protein oxidized in the cells in starvation is always the same. When there is no fat, protein may burn exclusively. From this it follows that *the quantity of the protein metabolism in starvation depends upon the amount of fat in the body.*

E. Voit[2] has prepared the following table from an experiment of Schöndorff[3] upon a fasting dog. The quotient $\frac{\text{N content}}{\text{Fat content}}$ gives the ratio between these two components of the organism at the time specified. The ratio $\frac{\text{Energy protein}}{\text{Energy total}}$ gives the percentage of the total energy derived from the protein metabolism. The dog died on the thirty-eighth day of his fast:

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[1] E. Voit: "Zeitschrift für Biologie," 1901, xli, 545.

[2] E. Voit: *Ibid.*, p. 520.

[3] Schöndorff: "Pflüger's Archiv," 1897, lxvii, 430.

PROTEIN METABOLISM IN STARVATION AS INFLUENCED BY THE FAT CONTENT OF THE ANIMAL

Starvation Day.	Weight in Kg.	$\frac{\text{N Content}}{\text{Fat Content.}}$	Excreta N in Grams.	Energy per Sq. Meter Surface.	$\frac{\text{Energy Protein}}{\text{Energy Total.}}$ Reduced to %.
1st to 3d.....	22.4	0.25	7.91	1040	26.5
4th to 13th...	20.7	0.29	5.38	974	16.2
14th to 15th..	19.7	0.34	5.70	959	18.1
16th to 23d. .	18.7	0.40	5.71	944	19.1
24th to 30th..	17.4	0.57	5.92	919	21.3
31st to 35th..	16.2	0.87	6.62	901	25.6
36th.........	15.7	1.19	7.41	889	29.5
37th.........	15.5	1.34	8.41	887	33.8
38th.........	15.2	1.51	8.89	881	36.6

E. Voit finds that the amount of protein metabolism depends so absolutely upon the relation between the amount of fat and protein in the body (the $\frac{\text{N content}}{\text{Fat content}}$) that, knowing this ratio, he says he can estimate the relative protein metabolism. When the ratio rises to 4.84 in the rabbit, then 98.3 per cent. of the total energy may be derived from protein. Had fat still been present in considerable quantity the protein metabolism would have remained low. This is the law which governs the gradual rise in the protein metabolism during starvation, the "premortal rise" it has been termed. The increased combustion of the protein is due to the requirement for energy in an organism which has a constantly decreasing amount of fat upon which to draw.

Zuntz[1] describes a dog which lived in a constant state of undernutrition for about a year. The energy requirement was as follows:

	Weight, Kg.	Calories per Square Meter.
Start..............................	10	931
Eleventh month......................	4.98	631
Twelfth month......................	4.1	921

Though the nitrogen in the urine was not collected, Zuntz considers it possible that with the utilization of body fat the metabolism of protein increased, and therefore the heat production increased (see p. 238) toward the end of life.

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[1] Zuntz: "Biochem. Zeitschr.," 1913, lv, 341.

The actual loss of body weight is greater when protein is the source of energy than when the energy is derived from fat. The metabolism of protein in 100 grams of flesh yields only 80 calories in contrast with 930 calories liberated when 100 grams of fat are oxidized. To obtain equivalent amounts of energy there must, therefore, be a destruction of eleven and a half times more "flesh" by weight than fat.

Rubner[1] has maintained a dog for a long period on a diet of fat which was sufficient in amount to cover the energy requirement. The content of body nitrogen fell from 358.3 grams to 166 grams, a loss of 53.7 per cent. Rubner finds that during the whole period the daily waste of nitrogen is 0.9 gram per 100 grams contained in the body. This "wear and tear" quota is therefore a function of the intensity of the life processes, being proportional to the amount of protoplasmic material present.

What is the cause of death from starvation? It does not seem to be due to an essential change in the composition of the cells themselves, for no chemical alteration has been detected in them.[2] What, then, is the cause of death? The general argument of E. Voit is as follows: It must be due either to a general failure of all the cells or injury of certain organs which are necessary for life. If the first cause were the true one, then death would take place when a certain definite percentage of protein loss occurred. This does not happen, since the body loss at the time of death may vary between 20 and 50 per cent. of its original protein content. When the genital organs of the salmon develop at the expense of the liquefying muscle substance brought them by the blood, not a single muscle cell of the fish is killed, even though these lose 55 per cent. of their protein in the process (Miescher). It seems extremely improbable, then, that a much smaller loss of protein in starvation can be the cause of general cellular death. On the other hand, if death be due to the failure of certain organs especially important to life, the cause is to be found in two factors:

[1] Rubner: "Archiv für Hygiene," 1908, lxvi, 49.

[2] Abderhalden, Bergell, and Doerpinghaus: "Zeitschrift für physiologische Chemie," 1904, xli, 153.

Either these organs receive too little nutrition for their proper functioning, or they become so emaciated that they fail in spite of sufficient nutriment. Either the fuel is insufficient or the machine wears out.

The following table gives some answer to this. The general arrangement is in the order of the greater original fat content of the animals:

INFLUENCE OF FAT CONTENT ON PROTEIN METABOLISM AND ON LENGTH OF LIFE IN STARVATION

ANIMAL.	FIRST WEIGHT, KG.	FAT IN %.		LOSS IN %.		DAYS BEFORE DEATH FROM STARVATION.	AUTHOR.
		Start	End.	Animal.	Body N.		
Dog	20.64	19	12	28	22	30	Falk.
Fowl	1.95	26	5	42	26	35	Schmanski.
Guinea-pig	0.67	16	10	38	26	10	Rubner.
Dog	23.05	11	1.7	34	35	38	Schöndorff.
Fowl	1.00	9.1	0.7	39	37	12	Kuckein.
Rabbit	1.51	7.1	0.4	49	49	19	Rubner.
Rabbit	2.53	6.3	0.5	44	49	19	Koll.
Rabbit	2.34	6.3	0.5	41	45	19	Rubner.
Fowl	1.89	2.7	0.7	34	41	9	Kuckein.
Rabbit	2.08	2.3	0.4	35	38	8	Kaufman.
Rabbit	2.99	2.3	0.3	32	35	9	Rubner.

In the first three animals a large amount of fat was present at the time of death, and this had prevented a great tissue waste. Abundant food was therefore available for the cells. The cause of death seems, therefore, to be due to a reduction of activity in one or more organs important for life.

Again, if the protein loss be kept down by administering protein in quantity insufficient for the heating demands of the organism, the animal is kept living largely on his own fat. Schulz[1] in this way kept two dogs alive for twenty-eight and thirty-eight days, with losses of body nitrogen amounting to only 18 and 7 per cent. of the original quantity. The fat present was only 0.4 to 0.5 per cent. at the end. These dogs certainly suffered from no general loss of cell tissue. E. Voit concludes *that death from starvation is primarily due to loss of*

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[1] Schulz: "Pflüger's Archiv," 1899, lxxvi, 379.

substance in organs important to life, but it may also ensue under certain circumstances as a result of deficient nutrition to these organs.

Schulz[1] and his pupils let a dog which was fat and well nourished fast for twenty-seven days. On the twenty-fifth day the animal manifested weakness, which, on the twenty-seventh day, appeared to threaten its life. Then for a day 400 c.c. of milk were given to the dog and on four subsequent days 300 grams of meat each day. Although these quantities of food were greatly under the quantity required to maintain the dog without loss of body fat, still the animal recovered its strength, added 7.3 grams of protein nitrogen to its body, and then lived during a second period of sixty-one days of starvation. During this second fasting period the protein metabolism was on a much lower level than during the first period. Schulz notices that when the fasting dog still contains considerable fat, protein in the food is readily retained, even though the content of energy ingested be under the body's needs. When, however, the body fat is nearly exhausted, all the ingested protein and some body protein besides is destroyed to provide for the support of the organism. Schulz concluded that death from starvation is due to autotoxemia, a condition which was relieved in the fasting experiment mentioned above by the ingestion of meat.

On the basis of their experiments Howe and Hawk[2] conclude that a "repeated fast" is accompanied by less protein loss from the body than an original fast. Thus, in one dog weighing originally 3.4 kilograms, death was threatened after 15 days of fasting, the loss of body weight having been 45.8 per cent. The animal was then given food for forty-seven days and brought back to the original weight, after which it fasted again and lost 46.8 per cent. in weight during thirty days. During the first fast the daily loss of body nitrogen was 2.3 grams and during the second, 1.31 grams.

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[1] Schulz: "Pflüger's Archiv," 1906, cxiv, 419–462.

[2] Howe and Hawk: "Journal of the American Chemical Society," 1911, xxxiii, 253.

The question of what organs are attacked in starvation has attracted attention. Long ago Voit[1] showed that the muscles of a cat which starved thirteen days lost 30 per cent., while heart, brain, and cord lost 3 per cent. only. In normally nourished animals E. Voit finds that the relative weights of the fat-free organs in animals of the same species are very constant. He[2] uses Kumagawa's[3] results to show what percentage the different organs represent in the fat-free organism of a dog before and after a twenty-four-day fast. The third column represents the precentage loss of the fat-free organ in starvation:

LOSS IN WEIGHT OF DIFFERENT ORGANS DURING STARVATION

Organ.	Fat-free Animal Contains in Percentage of Weight.		Fresh Fat-free Organ Loses in Percentage Weight During a 24 Days' Fast.
	Well Nourished.	Starvation.	
Skeleton	14.78	21.50	5
Skin	10.30	11.29	28
Muscles	53.77	48.39	42
Brain and cord	0.94	1.11	22
Eyes	0.11	0.16	3
Heart	0.54	0.69	16
Blood	7.14	5.69	48
Spleen	0.39	0.26	57
Liver	3.98	3.05	50
Pancreas	0.33	0.19	62
Kidney	0.66	0.45	55
Genitals	0.30	0.23	49
Stomach and intestine	5.81	6.02	32
Lungs	0.89	0.97	29

It is apparent that the greatest loss is from the glands and the least from the skeleton. The activity of the glands is greatly reduced in starvation. Luciani found that there was no gastric juice formed during Succi's thirty-day fast, but Langley and Edkins[4] find pepsinogen stored within the cells of a cat's gastric glands. The bile flow continues up to the death of the

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[1] Voit: "Zeitschrift für Biologie," 1866, ii, 353.

[2] E. Voit: *Ibid.*, 1905, xlvi, 195.

[3] Kumagawa: "Aus den Mittheil. d. med. Fakultät der kais. Japan. Univ.," Tokio, 1894, iii, 11.

[4] Langley and Edkins: "Journal of Physiology," 1886, vii, 371.

person, but in diminished quantity, corresponding to the lack of food and the decreasing size of the liver. The writer[1] has noticed a great reduction in the activity of the milk secretion in starving goats, there being a permanent cessation of flow after five days. The percentage of fat increases in the milk, as it does in the blood, liver, and other organs.[2] The fasting organs attract fat from the fat deposits of the body, and it is brought to them by the circulating blood. Glucose is present in the blood up to the last day of life, having its probable origin in a constant production of sugar in protein metabolism. The composition of the plasma of the blood in fasting, as regards its protein constituents, varies slightly from the normal. Lewinski[3] gives the following comparative analyses of blood-plasma of dogs:

100 C.C. BLOOD-PLASMA CONTAIN OF GRAMS N:

		Total.	Albumin.	Globulin.	Fibrinogen.
Dog I....	Fasting................	0.935	0.621	0.257	0.057
	Fed....................	0.831	0.511	0.240	0.080
Dog II...	Fasting................	0.921	0.313	0.544	0.064
	Fed....................	1.062	0.515	0.423	0.124
Dog III..	Fasting................	1.010	0.467	0.450	0.093
	Fed....................	0.977	0.475	0.402	0.100
	Fasting................	1.096	0.554	0.443	0.099
Dog IV...	Fasting................	1.052	0.536	0.324	0.192
	Fed....................	0.877	0.542	0.248	0.087

The only constant change seems to be a slight increase of globulin during fasting. Burckhardt believes this to be due to the passage of globulins from the tissues to the blood. Robertson[4] reports that in the fasting dog and cat the globulins tend to increase in the blood, whereas in the rabbit, ox, and horse the albumins increase. The percentage of hemoglobin and the number of blood-corpuscles are not appreciably affected. It is evident, then, that the blood in starvation retains the

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[1] Lusk: Voit's Festschrift, "Zeitschrift für Biologie," 1901, xlii, 41.

[2] Rosenfeld, "Ergebnisse der Physiologie," 1903, ii, 1, 50.

[3] Lewinski: "Pflüger's Archiv," 1903, c, 631.

[4] Robertson: "Journal of Biological Chemistry," 1912, xiii, 325.

normal composition as regards its nutrient materials, except that it carries fat in increased quantity to the cells. In general the cells are well nourished for the ordinary maintenance of the life functions. Hence the appetite is not an expression of general cellular hunger, but rather the result of a local condition of the gastro-intestinal canal, which stimulates the individual to replenishment.

The glycogen of an animal is greatly reduced during starvation, but after seventy-three days it is not entirely removed.[1] Prausnitz[2] reports that a dog weighing 22 kilograms, after fasting for twelve days and after excreting 287 grams of sugar in the urine as the result of phlorhizin injections, still contained 25 grams of glycogen in his body. The writer[3] has found 0.4 gram of glycogen in the liver of a meat-fed phlorhizinized dog after eleven days of diabetes and an excretion of over 600 grams of sugar. Exercise will greatly reduce the glycogen content, but the only method of completely freeing the organism of glycogen is by tetanus.[4] Zuntz[5] rid a rabbit of glycogen by strychnin convulsions and then kept the rabbit fasting and under the influence of chloral for 119 hours. During this time 5.25 grams of sugar were excreted in the urine, and yet 1.286 grams of glycogen were found in the liver and muscles. This must have gradually arisen from the protein metabolism. The writer[6] made an observation that in a fasting diabetic rabbit tetanus produced an extra elimination of sugar in the urine of 1.1 grams, which undoubtedly was derived from the glycogen content of the organism (see p. 458). The quantity eliminated corresponded to the amount found as glycogen by Zuntz, as above mentioned.

There now remains a discussion of the influence of work and of change in temperature upon the fasting organism.

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[1] Pflüger: "Pflüger's Archiv," 1907, cxix, 119.

[2] Prausnitz: "Zeitschrift für Biologie," 1892, xxix, 168.

[3] Reilly, Nolan, and Lusk: "American Jour. of Physiol.," 1898, i, 397.

[4] Külz: Ludwig's Festschrift, 1891, p. 119.

[5] Zuntz: Verhandl. der physiol. Ges. zu Berlin, "Arch. für Physiol.," 1893, p. 378.

[6] Lusk: "Zeitschrift für Biologie," 1898, xxxvi, 111.

Frentzel[1] has shown the effect of external work upon the protein metabolism of fasting dogs. One of the dogs did an amount of work corresponding to 216,937 kilogrammeters in three days. The protein metabolism rose during the working hours and continued high on the last day, which was one of complete rest. Frentzel computes that the nitrogen elimination of the last four days (= 20.7 grams) represents an energy equivalent of 220,300 kilogrammeters. This could not cover the work done by the dog if we add to the measured work that which was done by the heart and respiratory muscles. The protein metabolism of four days is therefore entirely insufficient to cover the work done during three. The source of the energy for the work accomplished must be found in an increased metabolism of fat. The increase in protein metabolism above that of rest was not sufficient to supply 7 per cent. of the energy needed to do the work. The record of the dog's nitrogen metabolism is as follows:

INFLUENCE OF WORK ON THE N METABOLISM OF FASTING DOGS

Day.	Work or Rest.	Food.	Grams of N Excreted.	
			Per Day.	Per Hour.
1st to 4th	Rest.	100 g. lard		
5th	Rest.	100 g. “	3.13	0.1304
6th	Rest.	100 g. “	3.52	0.1467
7th	Rest.	Fasting.	3.71	0.1546
8th	Rest.	“	3.99	0.1663
9th	Work.	“	4.97	0.3680* 0.1837†
10th	Work.	“	5.02	0.2750* 0.1960†
11th	Work.	“	5.63	0.2400* 0.2335†
12th	Rest.	“	5.08	0.2117

* Work. † Rest.

Succi did not show a similar rise of protein metabolism from the effect of work. The eleventh day of his fast he spent

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[1] Frentzel: "Pflüger's Archiv," 1897, lxviii, 212.

in bed. On the twelfth day he rode a horse for an hour and forty minutes, raced for eight minutes with some students, and gave an exhibition of fencing in the evening. During the day he walked 19,900 steps. The urinary nitrogen on the eleventh day (rest) was 7.88 grams; on the twelfth (work), 7.16; and on the days following 3.50, 5.33, 5.14, 5.05. The work done was evidently at the expense of increased metabolism of fat. That this is the case had already been demonstrated by Pettenkofer and Voit.[1] A fasting man at work showed no increase in his protein metabolism, but the quantity of fat burned rose enormously. This is shown by the following comparison of the number of grams of fat burned:

	Day 8 A. M. to 8 P. M.	Night. 8 P. M. to 8 A. M.
Rest during day	116 gm.	94 gm.
Work during nine hours of day period	312 gm.	70 gm.

The fat metabolism during the day of work is two-and-a-half times that of the resting day, and is presumably the source of the energy for the mechanical work accomplished. During the night following the working day the reduction of fat combustion as compared with the night before is due to more profound sleep.

Another phase of the effect of work is shown in the variation between the day and night metabolism of Tigerstedt's fasting medical student, J. A. The average carbon dioxid excretion in grams for two-hour periods during five days of fasting was as follows. The figures showing the elimination during the hours of sleep are printed in black:

	A. M.	P. M.					
Time	10–12	12–2	2–4	4–6	6–8	8–10	10–12
Carbon dioxid (grams)	54.8	57.2	54.1	57.8	59.5	66.4	**46.5**

	A. M.			
Time	12–2	2–4	4–6	6–8
Carbon dioxid (grams)	**37.5**	**39.1**	**40.7**	68.6

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[1] Pettenkofer and Voit: "Zeitschrift für Biologie," 1866, ii, 459; C. Voit: *Ibid.*, 1878, xiv, 144.

The nitrogen of the urine was also less during sleep than during the waking hours:

Fasting Day.	N in the Urine.	
	Day.	Night (10 P. M. to 10 A. M.).
1st	7.11	4.93
2d	6.87	5.85
3d	6.83	6.65
4th	7.91	5.65
5th	6.36	4.98

Johansson[1] finds that the inequality of night and day metabolism depends on muscular work. Sitting up raises the metabolism, and standing does so still more. Even when one lies in bed, restlessness during the day may increase the metabolism. Zuntz[2] was the first to mention the condition of absolute muscular rest as significant. Even when perfect muscular relaxation ensues there may still be influences, such as light on the retina or sounds, which may act reflexly on the organism and slightly increase the metabolism. Johansson illustrated these variations in the following comparisons between night and day excretion of carbon dioxid of starving men, the night CO_2 being figured at 100:

	Night CO_2.	Day CO_2.	Author.
Complete muscular rest	100	105	Johansson.
Ordinary rest in bed	100	110	Johansson.
Ordinary life (no hard work)	100	142	Tigerstedt.
" " " "	100	128	Pettenkofer and Voit.
" " " "	100	147	Tigerstedt.

Johansson agrees with Tigerstedt that the minimum metabolism of a man in bed is represented by 24 to 25 calories per kilogram daily, and results obtained by Zuntz, Loewy, and others lead to the same conclusion.[3]

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[1] Johansson: "Skan. Archiv für Physiologie," 1898, viii, 109.

[2] Lehmann and Zuntz: "Virchow's Archiv," 1893, cxxxi, Supplement, 26.

[3] Tigerstedt: "Skan. Archiv für Physiologie," 1910, xxiii, 302.

The temperature of the fasting organism is usually normal. Luciani found a normal temperature in Succi during his thirty-day fast. The temperature falls only a few days before death. Sondén and Tigerstedt[1] find that the diurnal variations persist

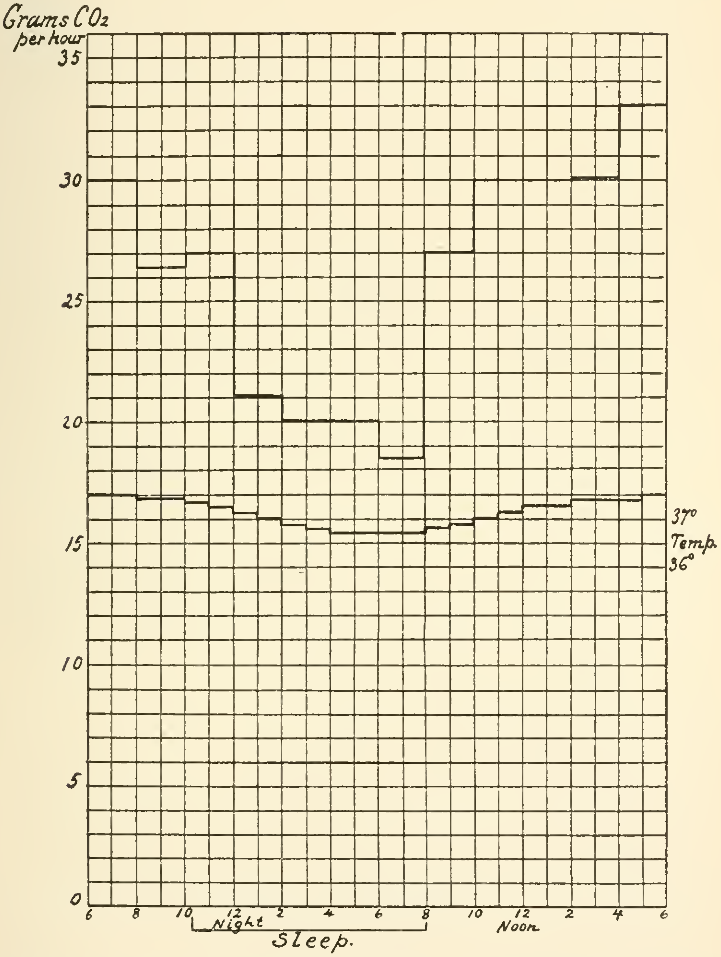

Fig. 5.—Curve of carbon dioxid elimination compared with Jürgensen's curve of normal diurnal temperature variation. This individual led a normal life and partook of his usual nourishment.

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[1] Sondén and Tigerstedt: "Skan. Archiv für Physiologie," 1895, vi, 136.

during fasting in their ordinary rhythm. The average temperature of the medical student J. A. during his five-day fast was but 0.16 degree below his normal temperature when food was allowed him. These diurnal variations are exactly concomitant with the fluctuations of carbon dioxid excretion noted on a previous page. When the carbon dioxid production increases, the temperature rises.

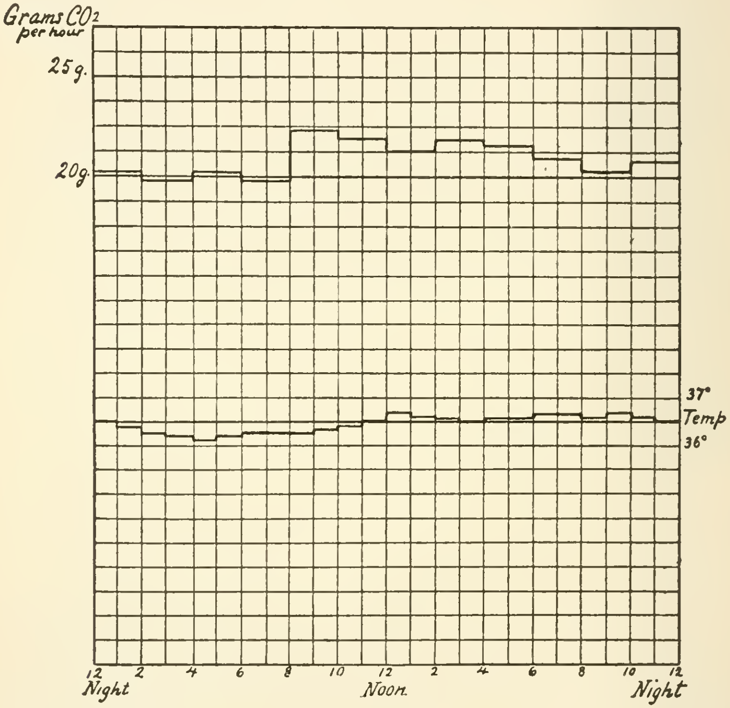

Fig. 6.—Carbon dioxid elimination and body temperature in fasting and complete muscular rest.

This parallelism may be easily shown by comparing the two factors in the chart (Fig. 5) as given by Sondén and Tigerstedt.[1] Furthermore, the diurnal variations tend to disappear if the person be kept in a state of muscular rest, so

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[1] Sondén and Tigerstedt: *Ibid.*, p. 132.

that the output of energy during the day and the night remains the same. In this state the temperature may fall 0.6 degree below the normal on account of the absence of muscle movement. This regularity of temperature and metabolism is beautifully shown in Fig. 6 taken from Johansson.[1]

Inversion of the normal routine of life, so that one sleeps in the daytime and is awake and active at night, brings about an inversion of the curve of body temperature. This is well shown in the monkey.[2]

Benedict,[3] however, was unable to obtain any inversion of the curve of normal body temperature in men who worked during the night and slept during the day.

Gibson[4] traveled half-way round the world in making a trip from New Haven, Connecticut, to Manila, and then returned. He found that the rhythm of daily variation was dependent on the time of the solar day and was independent of the part of the world in which he happened to be.

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[1] Johansson: *Loc. cit.*, p. 142.

[2] Galbraith and Simpson: Proceedings of the Physiological Society, "Jour. of Phys.," 1904, xxx, p. xx.

[3] Benedict: "Amer. Jour. of Phys.," 1904, xi, 145.

[4] Gibson: "Amer. Jour. of Med. Sci.," 1905, cxxix, 1049.

CHAPTER IV

THE REGULATION OF TEMPERATURE

It has been seen that the temperature of a warm-blooded animal is maintained at the normal throughout a fast. Not only this, but it is maintained at the same level, even though the temperature of the outside environment vary from 0° C. and lower to 30° to 35° C. In cold-blooded animals the temperature of the body is only slightly higher than that of their environment at the time. The metabolism of such animals varies with the temperature. The frog in the mud during the winter at a temperature of 4° C. has quite a different metabolism from that which he enjoys during the summer sunshine as he sits on the river-bank or snaps at passing flies. The curve of his carbon dioxid elimination at various temperatures has been made by E. Voit from the analyses of H. Schulz,[1] and is given below:

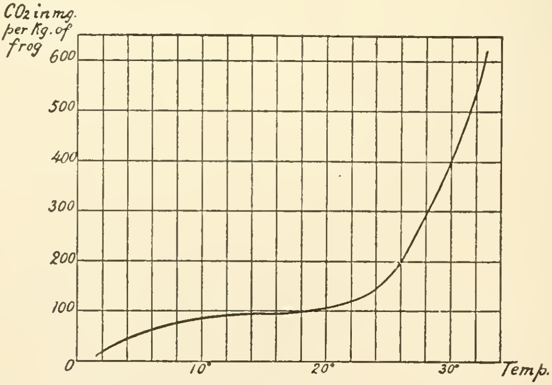

Fig. 7.—CO_2 in milligrams per hour per kg. frog.

Krogh[2] finds that the rise in the metabolism of the normal frog which appears at 20° C. does not show as sharp an ascent

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[1] Schulz: "Pflüger's Archiv," 1877, xiv, 78.

[2] Krogh: "Internat. Zeitschr. f. physik.-chem. Biologie," 1914, 1, 492.

in narcotized animals, indicating that in the normal frog nervous influences which produce tone begin to make themselves felt at this temperature.

Röhrig and Zuntz[1] first showed that a curarized mammal at ordinary room temperature lost the power of maintaining its body temperature, and the intensity of its metabolism decreased accordingly. Curare prevents the transmission of motor impulses to voluntary muscles.

Krogh states that the curve of oxygen absorption as influenced by body temperature is the same in the anesthetized frog and fish as in the curarized dog. One of Krogh's curves which is given here shows a sixfold increase of oxygen absorption in the curarized dog, indicated by a rise from 2.1 c.c. per minute at a body temperature of 14° C. to 13 c.c. per minute when the body temperature reached 37.2° C.

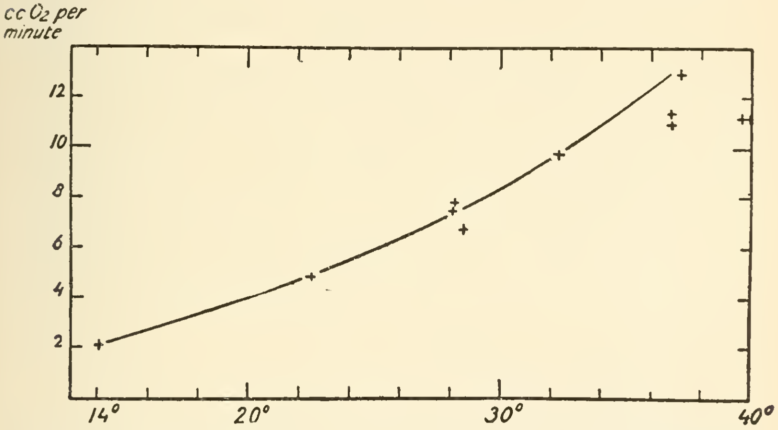

Fig. 8.—Curve of metabolism of a curarized dog subjected to different temperatures (after Krogh).

If the sciatic nerves of a curarized dog be severed, Mansfield and Lukacs[2] found that the heat production falls 10 or 15 per cent., but if the sympathetic nerves had previously been severed, cutting the sciatic was without influence upon

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[1] Röhrig and Zuntz: "Pflüger's Archiv," 1871, iv, 57.

[2] Mansfield and Lukács: "Pflüger's Archiv," 1915, clxi, 467.

metabolism. From this they conclude that in the curarized animal sympathetic nerves carry impulses which produce tone in muscles.

The reduction in activity which accompanies reduced body temperature is exemplified by the fact that a cat whose temperature has been artificially reduced to 19° C. may have but one heart-beat per minute.[1] At the time of hibernation the marmot lives at the expense of fat. The metabolism may correspond to only one-thirtieth the amount of energy used during the period of activity.[2]

Henriques[3] reports concerning the metabolism of a hedgehog awakening from the winter sleep. The animal weighed 660 grams. Tracheotomy was performed and the respiratory exchange determined during half-hour periods with five-minute intervals between periods, by the Zuntz method. The animal's body temperature was 6.5° C. in the rectum at the start, and the room temperature was 13° C. The animal remained quiet except for characteristic muscle movements resembling shivering which always accompany the awakening of hibernating animals.

The results were as follows:

Period.	I.	II.	III.	IV.	V.
R. Q.	0.62	0.70	0.72	0.71	0.70
Oxygen, c.c., hour and kg..	375	334	851	1983	2083
Rectal temperature at end	7.5°	9.0°	10.7°	14.1°	26.6° C.

Contrary to other authors, Henriques concludes that the awakening from winter sleep is usually at the expense of fat and not of carbohydrate.

During the entire period 2.21 liters of oxygen were absorbed by the animal. If this had been used for the oxidation of fat the heat produced would have been 10.40 calories (2.21 × 4.7 cals., see p. 61). At the conclusion of the experiment the animal was killed and placed in an ice calorimeter. It was found that the whole animal gave off 13.41 calories. At the

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[1] Simpson and Herring: "Journal of Physiology," 1905, xxxii, 305.

[2] Regnault and Reiset: "Annales de chem. et de physic," 1849, xxvi, 299.

[3] Henriques: "Skan. Archiv f. Physiol.," 1911, xxv, 15.

beginning of the experiment when the rectal temperature was 6.5° C. the hedgehog contained 3.56 calories (6.5° C. × 660 grams × 0.83 factor for specific heat of body). Therefore 9.85 calories were added to the body during the period of awakening, and these could have been obtained from the 10.40 calories derived from oxidation of fat and still leave a surplus of 0.55 calorie for loss of heat through radiation and conduction during the period when the body temperature was above the temperature of the environment. It should be remembered, however, that during the earlier periods of low body temperature the organism must have gained heat from its environment.

E. Voit[1] has drawn attention to the fact that a curve of increasing metabolism with increasing temperature corresponds to the increasing ability of muscle to contract, and to the increasing effectiveness of enzymotic activity. A high temperature is necessary for the irritability and activity of protoplasm. The warmth of the sunshine increases the irritability of the protoplasm of the tree in the spring, with the resulting development of the foliage. *Warmth, however, is not the cause of the metabolism, but only one of the conditions for it.* In warm-blooded animals the temperature is maintained at a constant level independent of climatic conditions, and this level is a favorable one for the activity of nerve and muscle. It would indeed be inconvenient were the active life of a man dependent upon the temperature of his environment. The essential mechanism for the regulation of the body temperature is nervous. The action of cold on the skin may stimulate its peripheral nerve-endings, which are sensitive to cold, and reflexly effect in the organism a greater heat production and a vasoconstriction of peripheral blood-vessels; the action of heat, on the contrary, effects vasodilatation and production of sweat. It is believed that the cold-blooded progenitors of warm-blooded animals changed their habitat from the sea to the land at a tropical temperature which is at present possessed by their descendants. In the course of

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[1] E. Voit: "Sitzungsber. der Ges. für Morph. und Physiol.," 1896, Heft III.

development these animals acquired the power to maintain that ancestral temperature which proved favorable for the activity of their body substance. The nervous mechanism through which this is accomplished is twofold: First, there is an increased production of heat in the presence of external cold (*the chemical regulation of temperature*); and, second, variations in the quantity of blood supplied to the skin modify loss of heat by radiation and conduction, and variations in the amount of sweat modify the loss of heat by evaporation of water (these are the factors of the *physical regulation of temperature*). The great importance of these two controlling influences will be seen as the subject develops.

If the body were a mass of cells having the shape of a ball with a constant heat production in its center, it would be easy to calculate its temperature in the different zones of the interior. The loss of heat from the surface would obviously be equal to the heat production if the temperature of the various zones continued constant.

If two balls of the same material, but of unequal size, were equally warm, the smaller would cool more quickly than the larger on account of the relatively greater exposed surface from which heat could be discharged. The heat elimination would be proportional to the surface exposed.

To determine the surface of geometrically similar solids, and hence of animals of similar shapes, the following formula was used by Meeh,[1] in which S = surface and V = volume:

$$\frac{S}{V^{\frac{2}{3}}} = \frac{S\sqrt[3]{V}}{V}$$

Since animals contain the same materials, one may substitute W = weight for V.

Then the value of $\frac{S\sqrt[3]{W}}{W}$ may be empirically determined for each shape or animal, and this value = k. Hence the formula would read:

$$\frac{S}{W^{\frac{2}{3}}} = k \text{ or } S = k\sqrt[3]{W^2}$$

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[1] Meeh: "Zeitschrift für Biologie," 1879, xv, 425.

The value of *k* or the constant in the relationship of weight in kilograms to surface in square meters in each animal has been given by Rubner as follows:

Man	12.3
Dog	11.2–10.3
Rabbit	12.9–12.0
Rabbit (without ears)	10.8
Calf	10.5
Sheep	12.1
Cat	9.9
Pig	8.7
Guinea-pig	8.5
Fowl	10.4
Rat	9.1
White mouse	11.4

To compute the body surface of a man, for example, the formula $12.3\sqrt[3]{(\text{body-weight})^2}$ would be employed.

The use of the above formula rendered possible the calculation of the heat elimination per unit of area in fasting animals during periods of twenty-four hours when the temperature of the environment is 15° C. and when moderate voluntary movements are permitted. When the subjects have been previously well fed, and are not emaciated, there is a surprising uniformity of result. It is Rubner's law that the metabolism is proportional to the superficial area of an animal.

Erwin Voit[1] has calculated the following general table showing the heat production in resting animals of various sizes at medium temperatures of the environment:

		Calories Produced	
	Weight in Kg.	Per Kilo.	Per Sq. M. Surface.
Horse	441	11.3	948
Pig	128	19.1	1078
Man	64.3	32.1	1042
Dog	15.2	51.5	1039
Rabbit	2.3	75.1	776
Goose	3.5	66.7	969
Fowl	2.0	71.0	943
Mouse[2]	0.018	212.0	1188
Rabbit[2] (without ears)	2.3	75.1	917

The universality of this law of Rubner's is remarkable. Even at a room temperature of 30° C. where all thermal influ-

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[1] E. Voit: "Zeitschrift für Biologie," 1901, xli, 120.

[2] Rubner: "Energiegesetze," 1902, p. 282.

ence is removed, two guinea-pigs of different sizes will produce heat in proportion to their surface. In this case there is a minimum of heat production determined for the resting organism according to the law of superficial area.

When this discovery was first made, the interpretation was offered that the variation in the metabolism of different animals in proportion to the skin area was due to the "chemical regulation" brought about by the specific sensory influences of cold proceeding from a definite area of surface. Before this Regnault and Reiset had noted that the heat production of sparrows per unit of weight was tenfold that of fowls, a phenomenon which they asserted was due to the fact that the smaller animals present a relatively larger surface to the surrounding air and thereby experience a considerable chilling, with the consequent generation of sufficient heat to maintain the normal body temperature. This explanation fell when Rubner discovered that at a temperature of 30° C., under which condition all thermal stimulus to the organism ceased, two guinea-pigs of different sizes still produced heat in proportion to their skin areas. A similar fact was noted by Frank and Voit,[1] who found that the administration of curare, which paralyzes the voluntary muscles, scarcely affected the carbon dioxid output of a dog as compared with what was eliminated during ordinary muscular rest, provided the temperature of the animal was maintained at the normal by keeping him in a warmed chamber. The mass of living cells preserved the same metabolism as before, even though a pathway of heat increase had been cut off through paralysis by curare of the motor nerve-endings in the muscles. Keeping the animal in a warmed chamber was necessary in this case, for Röhrig and Zuntz[2] had shown that curarized animals at the ordinary room temperature lost the power of maintaining their body temperature and that their metabolism decreased accordingly. The removal of the chemical regulation caused a behavior

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[1] Frank and Voit: "Zeitschrift für Biologie," 1901, xlii, 309.

[2] Röhrig and Zuntz: "Pflüger's Archiv," 1871, iv, 57.

toward external temperature similar to that of cold-blooded animals.

Although the effect of cold on the skin (inducing chemical regulation) is of itself demonstrably insufficient to account for the "law of skin area," Rubner[1] argues that even at 30° C., when the body is losing heat by means of the dilatation of the blood-vessels and the evaporation of water (physical regulation), the law is still a necessity if the general mechanism for loss of heat in the various animals is the same in all. An infant produces 90 calories per kilogram in twenty-four hours; an adult, 32 calories. Were the metabolism of an adult 90 calories per kilogram, the means of heat elimination through his comparatively smaller surface would have to be materially modified if a normal temperature were to be maintained with comfort.

Further analysis showed Rubner[2] that this evenness of heat production per unit of body surface was not due to any relation between the area of body surface and the area of cell surface within the organism.

Rubner estimates that a man weighing 60 kilograms contains 37.8 kilograms of cell mass, of which 40 per cent. is in muscle tissue, and that while the absorptive surface of the intestinal tract is 1.5 square meters, the surface area of the body cells amounts to 9014 square meters (2.2 acres). There are in 1 kilogram of body weight of man 150.2 square meters of such surface, and each square meter of cell surface produces at least 0.2 calorie per day. In the newborn mouse each square meter of cell surface produces eleven times this amount, or 2.2 calories. It is of interest, also, to note that a kilogram of yeast cells presents a surface area of 600 square meters and at a temperature of 38° C., or that at which mammalian cells exist, 1.25 calories per square meter of surface are produced in twenty-four hours, 8.34 grams of cane-sugar undergoing inversion and fermentation during that interval.

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[1] Rubner: "Energiegesetze," 1902, p. 174.

[2] Rubner: "Archiv für Physiologie," 1913, p. 240.

This reaction is independent of the strength of the sugar solution within the wide limits of 2.5 to 20 per cent. If the strength of the solution be at the maximum of normal reaction, or 20 per cent., the quantity of sugar utilized in twenty-four hours would be contained in a film $\frac{4}{100}$ millimeter in thickness surrounding the cells. A like analysis shows that in man, whose cells are bathed in a medium containing 0.1 per cent. of sugar, the quantity necessary for the support of life during one day would be contained in a layer which if spread around the cell would be $\frac{5}{100}$ millimeter in thickness.

From the calculation of the energy requirement in the food for the life of a man to the energy liberated by a yeast cell in its simple resolution of sugar into alcohol and carbon dioxid is indeed a far cry, except as showing that the energy doctrine, as enunciated by Rubner, unites the world of living things.

Magnus-Levy[1] made 41 short time respiration experiments on the same man when resting without food. The greatest variations from the mean were -7 and $+10$ per cent. The calories per square meter per twenty-four hours were 812. In 1912 Lusk[2] calculated that the heat production of three quiet and sleeping dogs was 759, 748, and 746 calories per square meter of surface at an environmental temperature of 26° C., that a dwarf produced 775 calories per square meter of surface, and that four out of five sleeping men investigated by Benedict showed an average heat production of 789 calories per unit of area. Only in the sleeping infant 7 months old, investigated by Howland, did the metabolism appear out of the ordinary and reached a level of 1100 calories, and this factor was specifically pointed out as indicating a higher metabolism in the youthful protoplasm than is present in the adult.

The critical studies of F. G. Benedict[3] led him to conclude "that the metabolism or heat output of the human body, even

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[1] Magnus-Levy: "Pflüger's Archiv," 1894, lv, 1.

[2] Lusk (with McCrudden): "Journal of Biological Chemistry," 1913, xiii, 450.

[3] Benedict, F. G.: "Journal of Biological Chemistry," 1915, xx, 298.

at rest, does not depend on Newton's law of cooling,[1] and is, therefore, not proportional to the body surface."

That a greater metabolism is induced in man after the ingestion of a liter of cold milk than after taking the same amount when it is warm, was shown in Tangl's[2] laboratory, and indicates that an influence may be exerted by cooling. The body temperature fell 0.25 to 0.8 degree. That such an influence is exerted by cooling was clearly demonstrated by Lusk,[3] who compared the heat production after giving glucose dissolved in cold water and in water at the body temperature to a dog placed in a calorimeter, with the following results:

Glucose in Cold Tap-water.		Glucose in Water at 38° C.	
Indirect.	Direct.	Indirect.	Direct.
Calories. 80.33	Calories. 75.19*	Calories. 75.92	Calories. 76.39

* Plus heat for warming the cold water.

When warm water was ingested the computed heat production agreed with that actually found, but when cold water was given there was an increased oxidation, as shown by indirect calorimetry, in order to provide for the body heat lost to the fluid in the stomach (see p. 132).

Benedict is in agreement with Carl Voit when he concludes that the mass of active protoplasmic tissue determines the height of the metabolism. However, in the search for a standard upon which to calculate what would be the normal heat production of a man suffering from disease it is obviously impossible to measure the mass of active protoplasmic tissue.

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[1] This law reads, "The quantity of heat gained or lost by a body in a second is proportional to the difference between its temperature and that of the surrounding medium" At the higher temperatures of environment it is obvious this law does not control. See Rubner's experiments on guinea-pigs, p. 120, demonstrating that the effect of cold on the skin is not a sufficient explanation of the law of skin area.

[2] Hári and von Pesthy: "Biochemische Zeitschrift," 1912, xliv, 6.

[3] Lusk: "Journal of Biological Chemistry," 1915, xx, 578.

When the Russell Sage Institute of Pathology constructed in Bellevue Hospital an Atwater-Rosa calorimeter copied in the main after the successful models of Benedict, it became absolutely essential that some criterion of normal metabolism be established as a basis from which one could estimate whether the metabolism of a patient under investigation was higher or lower than the normal. The severe criticisms of Benedict upon the method of estimating heat production from the unit of surface led to a very careful review of all the evidence and to new experiments. Du Bois,[1] who took up this work, has used an accurate and ingenious method with which he has been able actually to measure the surface area of normal men. He covered the body surface with tight-fitting underwear, applied melted paraffin, and then paper strips to prevent change in area when the covering was removed. This model of the surface when cut into flat pieces was photographed upon paper in which equal areas were of equal weight. From the weight of paper which received the photographic impression the area of body surface could readily be calculated. A round ball having an area of 0.1490 square meter, when measured by this method, gave an area of 0.1488 square meter. After this fashion E. F. and Delafield Du Bois have discovered that the formula heretofore used for estimating the surface area in man showed an average inaccuracy of 16 per cent. and a maximal variation from the normal of 36 per cent., this being found in very fat individuals. Two new formulæ, a "linear" and a "height-weight" formula, have been evolved which give an average variation of ± 1.5 per cent. and a maximal variation of ± 5 per cent. Using the older formula of Meeh, the heat production per square meter of surface is 833 calories during twenty-four hours, but using the more accurate formula of Du Bois this rises 16 per cent. to 953 calories. In normal adults of various shapes and sizes this is the *basal metabolism* as measured when the individ-

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[1] Du Bois, D. and E. F.: "Archives of Internal Medicine," 1915, xv, 868; *Ibid.*, 1916, xvii, 863.

ual is resting and before the administration of food in the morning.

The following table presents the results of work upon those persons whose surface areas were actually measured:

COMPARISON OF AREA OF BODY IN SQUARE METERS AS ACTUALLY MEASURED WITH THAT CALCULATED FROM THE DU BOIS FORMULA

Person.	Area. Measured.	Area Calculated.	Error in Du Bois Formula.	Error with Meeh's Formula.	Age.	Weight.	Height.	Basal Calories per Sq. M. Surface per Hour.	Remarks.
Men:	Sq. M.	Sq. M.	%	%	Years.	Kg.	Cm.		
Benny L......	0.8473	0.8512	+0.5	+21	36	24.2	110.3	33.0	A cretin.
Morris S......	1.6720	1.6938	+1.3	+17	21	64.0	164.3	41.2	Normal.
R. H. H......	1.8375	1.7680	−3.8	+ 7	22	64.1	178.0	40.9	Normal.
E. F. D. B....	1.9000	1.8832	+0.9	+14	32	74.0	179.2	39.8	Normal.
Gerald S......	1.4901	1.4941	+0.3	+ 4.9	17	45.2	171.8	36.7	Diabetes.
R. H. S	1.7981	1.7995	+0.1	+ 8.4	21	63.0	184.2	37.4	Normal.
Fabian S......	1.1869	1.1455	−3.5	+ 6.2	12	32.7	141.5		
R. L. (Legless)	1.4299	1.4692	+2.7	+37.0	43	63.8			
Women:									
Mrs. McK....	1.8592	1.8956	+2.0	+36	48	93.0	149.7	37.9	Very fat.
Emma W.....	1.6451	1.6128	−2.0	+11.6	26	57.6	164.8	33.3	Normal.
Child:									
Anna M......	0.3699	0.3592	−2.9	+ 9.3	2	6.3	73.2		

As the "Linear Formula" involved taking 19 measurements, a simpler procedure was sought. The formula $A = W^{\frac{1}{2}} \times H^{\frac{1}{2}} \times 167.2$, in which A = area in square meters, W = weight in kilograms, and H = height in centimeters, was found to give an average error of 2.2 per cent. The average error could be reduced to 1.7 per cent. by using the formula,

$$A = W^{0.425} \times H^{0.725} \times 71.84$$

Based on this formula a chart[1] has been devised by which it is possible to estimate the surface area at a glance. It is reproduced in Fig. 9.

The old formula of Meeh gives a close approximation to 34.7 calories per square meter of surface per hour as the meas-

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[1] Du Bois, D. and E. F.: "Archives of Internal Medicine," 1916, xvii, 863.

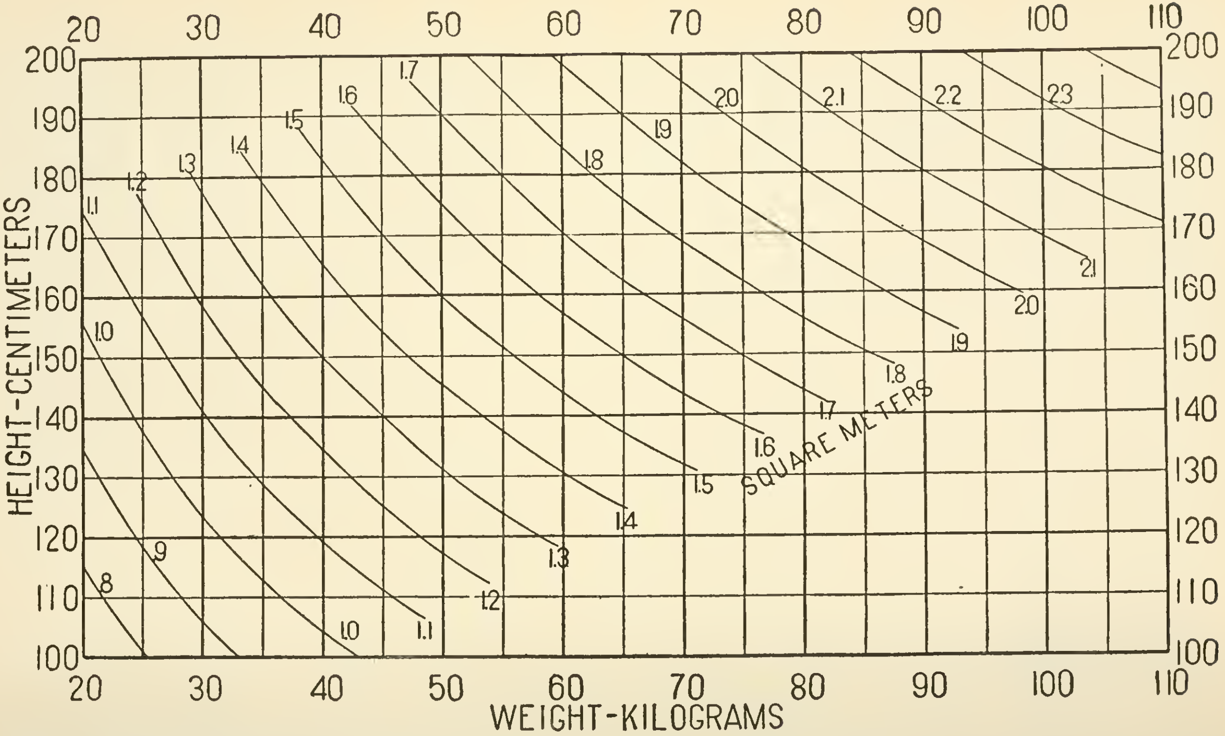

Fig. 9.—Chart for determining surface area of man in square meters from weight in kilograms (Wt.) and height in centimeters (Ht.) according to the formula: Area (Sq. Cm.) = Wt. $^{0.425}$ × Ht. $^{0.725}$ × 71.84.

ure of the basal metabolism. In people of normal shape this result is so constant that it justifies the conclusion that the basal heat production can be determined by Meeh's formula, whether Meeh's formula for determining surface area is correct or not.

The new formula gives the following results, the subjects being men between the ages of twenty and fifty years:

	Average Calories per Sq. Meter per Hour.	Maximum Variation from Average in Per Cent.
Average 9 normal controls (Du Bois[1])	39.7	+4 and −6
Average 9 normal controls (Means[2])	39.6	+7.6 and −7.1
Average 82 normal controls (Benedict[3])	38.9	usually ±10

As the results of Du Bois were obtained with calorimeter experiments of two or three hours' duration, the figure 39.7 calories per square meter of body surface per hour may be accepted as closely approximating the normal basal heat production of adult men. The experiments of Means and of Benedict were accomplished with the Benedict unit apparatus and bring confirmatory evidence.

Boothby[4] finds that the metabolisms of 23 patients who recovered their health after operations, and who had been confined in the hospital between twenty and fifty days, most of the time in bed, were within ± 10 per cent. of the Du Bois normal standard. This establishes the validity of the use of this measure of the basal metabolism as a criterion of an altered metabolism in hospital patients.

Du Bois[5] presents the following standards of basal metabolism with regard to age and sex. Figure 10 gives a graphic presentation of the data as applied to men.

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[1] Gephart and Du Bois: "Archives of Internal Medicine," 1916, xvii, 902.

[2] Means: "Journal of Medical Research," 1915, xxxii, 121; "Journal of Biological Chemistry," 1915, xxi, 263.

[3] Benedict, Emmes, Roth, and Smith: "Journal of Biological Chemistry," 1914, xviii, 139.

[4] Boothby: Oral communication, published by permission.

[5] Du Bois: "Archives of Internal Medicine," 1916, xvii, 887, and Aub and Du Bois, unpublished.

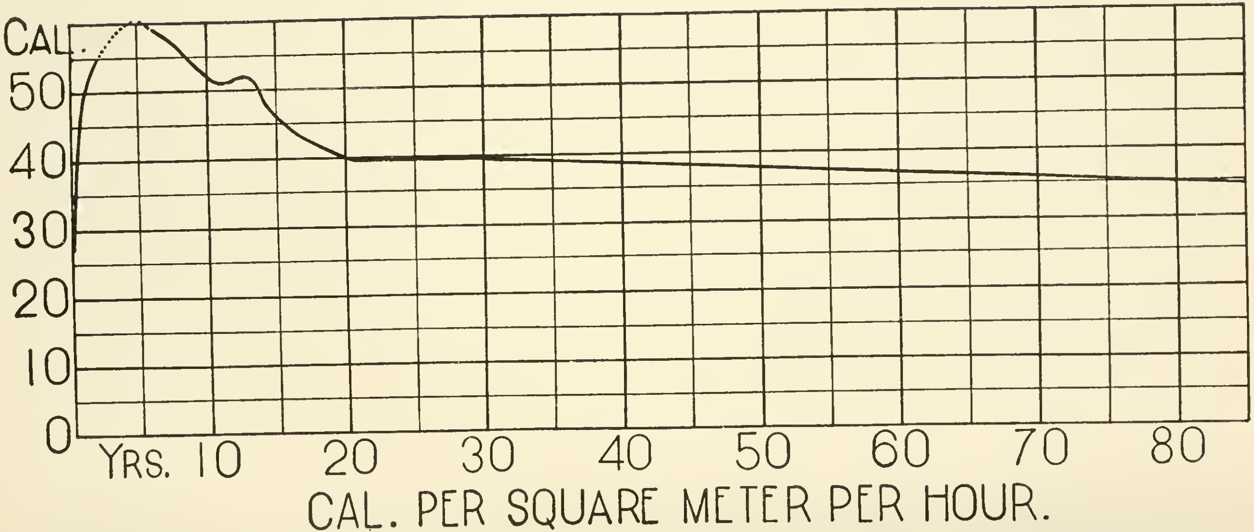

Fig. 10.—This chart, prepared by Du Bois, shows the basal metabolism as measured in calories produced per square meter of body surface per hour from birth until the age of eighty-five years in human males. Between maturity and the eighty-fifth year there is a gradual fall in the intensity of metabolism of 13 per cent. For consideration of the earlier part of the curve, see p. 406.

SUBJECTS.	AGE IN YEARS.	CALORIES PER HOUR PER SQUARE METER.	
		MEEH.	DU BOIS (HEIGHT-WEIGHT).
Boys	12–13	45.7	49.9
Men	20–50	34.7	39.7
Women	20–50	32.3	36.9
Men	50–60	30.8	35.2
Women	50–60	28.7	32.7
Men	77–83	....	35.1

The table shows that boys just before puberty have a high metabolism (see p. 559), that men have a higher metabolism than women, and that with advancing age there is no longer the same intensity of oxidation as in the prime of life.

The greater validity of the Du Bois formula over that of Meeh is shown in the following comparison by Du Bois of the metabolism of fat and thin subjects, computed in larger part from the work of Benedict, Emmes, Roth, and Smith:

	NUMBER OF SUBJECTS.	CALORIES PER SQ. METER AVERAGE VARIATION FROM NORMAL STANDARD IN PER CENT.		CALORIES PER KILOGRAM IN TWENTY-FOUR HOURS.
		MEEH.	DU BOIS.	
Fat men	5	−7.6	−4.0	21.9
Thin men	4	+6.4	−5.0	29.0
Fat women	7	−12.2	0.	19.4
Thin women	6	+4.2	−4.0	29.1

It is evident from this analysis that although thin women produce about 50 per cent. more heat per kilogram of body substance than their obese companions, yet per square meter of surface there is little difference.

The metabolism of a fat boy and his thin brother follow the same rule (see p. 257). Tangl[1] obtained the following results with pigs:

WEIGHT IN KG.	CALORIES IN TWENTY-FOUR HOURS:	
	PER KG.	PER SQ. METER (MEEH).
121	19.6	1060
49	27.2	1100

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[1] Tangl: Biochemische Zeitschrift," 1912, xliv, 252.

For the study of metabolism processes it is certainly most fortunate that the unit of surface area eliminates the same amount of heat in the normal adult within 10 per cent. of a determined average. The reason is not clear. But the reasons why the body temperature is constant or why the menstrual period is exactly timed are also not clear, though as facts they are established.

Recent experiments by Moulton[1] show that the nitrogen content of cattle is almost exactly proportional to the surface area of the animal. If the nitrogen content be a measure of protoplasmic tissue, these experiments afford a striking confirmation of the doctrine of Voit that the heat production is proportional to the mass of living cells (see p. 45).

However, the remarkable experiments of Grafe and Graham[2] appear to indicate that notwithstanding a large addition of protein to the organism of a dog following fasting, there is no increase in the fundamental metabolism. These experiments are summarized below:

Date.		Weight in Kg.	± N to Body.	Calories in Diet.	Calories of Metabolism.		Hours After Last Food.
					Total.	Per Sq. M.	
X, 25	Last day of food.	20.15	......	....	1056	1326	12
XI, 14	21st fasting day.	15.00	−83.5	....	672	1028	
XI, 18	3d day of food.	18.50	−48.6	2244	816	1036	12
XI, 22	7th day of food.	20.00	+4.7	2244	1081	1364	10
XI, 28	13th day of food.	20.05	+79.7	2580	973	1227	36
XII, 31	46th day of food.	20.25	+265.8	1660	1112	1396	36

After seven days of food the animal recovered all the weight and nitrogen lost during twenty-one days of fasting and its heat production was as before the fast. (See also p. 211.)

The organism, therefore, preserves the tropical temperature of its cells at the expense of a metabolism which is proportional to the skin area of the individual.

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[1] Moulton: "Journal of Biological Chemistry," 1916, xxiv, 299.

[2] Grafe and Graham: "Zeitschrift für physiologische Chemie," 1911, lxxiii, 1.

The loss of heat by an organism at rest follows these paths:

1. Conduction and radiation.
2. Evaporation of water from lungs and skin.
3. Warming the food ingested.
4. Warming the inspired air (conduction).

The great outlets for heat loss are by conduction and radiation (of which in the dog 97.3 per cent. takes place through the skin and 2.7 per cent. through the lungs[1]) and through the evaporation of water. The losses through warming the food, and through heat of the urine and of solution of urinary constituents through the feces, and the warming of expired carbon dioxid may be ordinarily disregarded.

The pathway for the loss of heat varies with the temperature of the environment. At a low temperature there is little evaporation of water, and at a temperature of 37° C. there can be no heat loss by radiation and conduction (except by a rise in body temperature), and water evaporation removes the whole of it. In the dog at a high temperature there is spreading out of the limbs to promote heat loss by radiation and conduction, and rapid breathing (polypnea) with extension of the hyperemic tongue to promote evaporation of water. In the horse and in man there is especially an outbreak of sweat which is not possible in the dog, as its skin does not secrete sweat.

Du Bois[2] finds that the average loss of water from the lungs and skin is 680 grams per day in the normal resting man at an environmental temperature of 23° C. and medium humidity. The evaporation of this amount of water represents an absorption of heat equal to 24 per cent. of the total heat loss. This latter figure is in exact agreement with an average of results previously reported by Benedict and Carpenter.[3] According to Loewy[4] the loss of water of perspira-

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[1] Rubner: "Energiegesetze," 1902, p. 187.

[2] Gephart and Du Bois: "Archives of Internal Medicine," 1916, xvii, 902.

[3] Benedict, F. G., and Carpenter: Carnegie Institution of Washington, Publication 126, 1910.

[4] Loewy: "Biochemische Zeitschrift," 1914, lxvii, 243.

tion per square meter of body surface is greatest in the arms, next greatest in the legs (the extremities yielding not far from 75 per cent. of the total), and least from the trunk. The greatest actual loss is, however, from the legs.

Loewy also finds that in men without sweat-glands the evaporation of water from the skin may amount in maximo to 15.6 grams per square meter per hour, or 800 grams for the whole body during a day. Vasomotor reflexes may play an important part in the quantity of water evaporated. Placing the right forearm in cold water reduced the water elimination from the right leg from 3.64 to 3.22 grams per square meter of surface per hour. Washing the right arm with alcohol and ether reduced the water elimination of the right leg to 1.78 grams for the same unit of measurement. In both of these experiments the leg showed an increase above the normal evaporation of water after the removal of the stimulus of cold from the arm.

Generally speaking, there is little difference between the temperature of the inner organs of the body. Heidenhain,[1] confirming earlier work of Claude Bernard, found that in 84 out of 94 experiments with dogs the temperature of the right ventricle was higher than that of the left, two-thirds of the cases showing differences between 0.1° to 0.3°. Claude Bernard[2] states that during digestion the blood of the hepatic vein is 0.1° higher than that of the portal vein. Quincke[3] found that the temperature of the empty stomach of a boy was constantly 0.12° higher than the rectal temperature, and that after the ingestion of 500 c.c. of water at a temperature of 20° C. the original temperature was not regained for seventy to seventy-five minutes. Rancken and Tigerstedt[4] find a temperature in the stomach of a boy with a gastric fistula which averages 0.09° higher and is in maximo 0.2° higher than that of the rectum.

[1] Heidenhain: "Pflüger's Archiv," 1871, iv, 558.
[2] Bernard: "Leçons de physiologie opératoire," Paris, 1879, p. 481.
[3] Quincke: "Archiv für exp. Path. und Pharm.," 1889, xxv, 375.
[4] Rancken and Tigerstedt: "Skan. Archiv für Physiologie," 1909, xxi, 85.

Regarding the surface temperature, Henriques and Hansen[1] report the following temperatures at different depths in the fat of the hog's back just one side of the median line:

	C.
1 cm. under the skin	33.7°
2 “ “ “	34.8°
3 “ “ “	37.0°
4 “ “ “	39.0°
Rectal temperature	39.9°

The environmental temperature was, unfortunately, not noted. It must be evident that under these conditions blood coming from the internal organs must lose heat to the cooler surface of the organism.

Benedict and Slack[2] studied the simultaneous records of rectum, vagina, axilla, breast, groin, hand, arm, and mouth, and concluded that aside from the skin temperature a rise or fall in rectal temperature is accompanied by a corresponding rise and fall in temperature of all other parts of the body in man.

Coleman and Du Bois[3] find that in fever, under conditions of a changing blood-supply to the skin, well-covered surface thermometers give a more accurate indication of the average change in body temperature than does the rectal thermometer. As the measurement of the amount of heat gained or lost by an organism during an experiment in which direct calorimetry is determined is effected through the observation of the changes of body temperature, this is an important matter. It may be stated as a general principle that when there is a wide variation in rectal temperature direct and indirect calorimetry do not usually agree as closely as when there is little alteration in body temperature, which indicates that the blood is not at all times so distributed throughout the body that the average rise throughout all the parts is equal to the rise in the rec-

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[1] Henriques and Hansen: "Skan. Archiv für Physiologie," 1901, xi, 161.

[2] Benedict and Slack: Carnegie Institution of Washington, Publication 155, 1911.

[3] Coleman and Du Bois: "Archives of Internal Medicine," 1915, xv, 887.

tum alone. Yet, on the whole, the rectal temperature is the best guide available.

Some idea of the activity of the blood flow which equalizes the body temperature may be obtained from the observations of Burton-Opitz,[1] from which may be calculated that an amount of blood equal to the entire amount in the body of a dog traverses the liver every three minutes.

It has been seen that Lavoisier noticed that cold increases the metabolism. This has been abundantly confirmed. The simplest illustration of this action is to be found in fasting animals. Rubner has called this increase of metabolism and, therefore, of heat production the *chemical regulation* of the body temperature (see p. 118). It is the same as burning more coal in the furnace on a cold day in order to maintain the temperature of the house. Voit had previously demonstrated this action in the case of a man (see below).

It has been noted that a constant basic quantity of energy is necessary to maintain the life-processes of a warm-blooded animal situated in a tropical environment. In this case the *energy* of metabolism is directly concerned in maintaining the vibrant motions of the molecules of protoplasm (see p. 301) and heat production is a secondary result. If, now, the organism be subjected to the influence of a cold environment, there is an increased production of *heat* which is directly derived from metabolized substances and the mission of which is to maintain the temperature of the body at the tropical point. It will also be shown in another place how this passive increase in heat production through "chemical regulation," which is induced without visible motion on the part of the animal, may become unnecessary if instead the needed heat be obtained from other sources, as from the increased heat production incident to muscular work or to food ingestion.

Rubner placed a fasting guinea-pig in a bell-jar which was ventilated so that the carbon dioxid production could be

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[1] Burton-Opitz: "Quarterly Journal of Experimental Physiology," 1912, v, 189.

determined. The temperature of the bell-jar could be changed by immersing it in water. The following were the results:

ACTION OF CHEMICAL REGULATION IN THE GUINEA-PIG

Temperature of Air.	Temperature of Animal.	Grams of CO_2 in One Hour per Kg. Animal.	Percentage Change of CO_2 for Each 1° C. Rise in Temperature of Air.
0.0°	37.0	2.905	−2.33
11.1°	37.2	2.151	
20.8°	37.4	1.766	−1.84
25.7°	37.0	1.540	−2.67
30.3°	37.7	1.317	
34.9°	38.2	1.273	−0.71
40.0°	39.5	1.454	+2.82

It is evident from the table that there was a constant decrease in the metabolism as the air was warmed from 0° to 35° C. The metabolism at 0° was two and a half times that at 30°, an increase as pronounced as is incurred as the result of severe muscular work. The animal at 0° was not observed to move around any more than he did at 30°. These results have been confirmed by Murschhauser.[1] Other experiments confirmed Rubner in the view that the *critical temperature*, or the temperature of the minimum metabolism, lay at 33°. At this point temperature had the least influence on total metabolism. When the temperature is raised from 30° there is at first no increase in the metabolism. This is due to the action of the apparatus for the *physical regulation* of body temperature. As the temperature rises the blood-vessels of the skin become dilated and the evaporation of water from the body is promoted. These factors tend to maintain the normal temperature of the organism by physical means. If the temperature of the air be high, so that the physical regulation be not sufficient to cool the body, then a supernormal temperature ensues. Such a febrile temperature raises the metabolism by warming the cells, as is seen in the table of the experiment in which the guinea-pig was exposed to a temperature of 40°. The range of the physical regulation—that is, the period

[1] Murschhauser: "Zeitschrift für physiologische Chemie," 1912, lxxix, 301.

during which external temperature change does not alter metabolism—depends, according to Rubner, on the natural protections which an animal possesses which insure him against heat loss. These are two in number—the hairy covering and the thickness of the layer of subcutaneous fat.

Rubner has shown that the hair of the black cat, black lamb, rabbit, skunk, raccoon, mink, musk-deer, and sheep is of itself relatively light in weight, but that the fur contains a very large quantity of air. The whole of the fur covering of these animals consists of between 97.3 and 98.8 per cent. of air. The fur, therefore, really consists of air with between 1.2 and 2.7 per cent. of hair. The slight conductivity of the fur is principally dependent on this layer of stationary air. If an animal be covered with a fur containing this stagnant air, he will be better protected from loss of heat than if he had none, and also less susceptible to the influence of cold upon the surface of his skin. This protective covering therefore extends the range of the physical regulation.

Rubner[1] gives the following experiment showing the influence of temperature on a small fasting dog with long hair:

ACTION OF CHEMICAL REGULATION IN THE DOG

Day.	N in Urine.	N in Feces.	Total N.	C of Respiration.	C of Urine.	Total C.	C from Fat.	Calories from Protein.	Calories from Fat.	Total Calories.	Temperature.
1st.......	1.80	0.06	1.86	20.0	1.1	21.0	14.9	46.5	183.6	230.1	20.0°
2d.......	1.56	0.06	1.62	22.4	1.0	23.4	18.0	40.4	224.6	264.6	15.2°
3d.......	1.52	0.06	1.58	28.2	1.0	29.1	23.9	39.5	294.7	334.2	7.6°
4th.......	1.56	0.06	1.62	18.9	1.0	19.9	14.5	40.5	179.0	219.5	30.0°
5th.......	1.42	0.06	1.48	17.3	0.9	18.2	13.7	37.0	169.3	206.3	25.2°

One observation was made in this experiment on the dog which was not possible in the case of the guinea-pig, and that

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[1] Rubner: "Die Gesetze des Energieverbrauchs," 1902, p. 105.

concerned the nitrogen excretion. The nitrogen excretion for twenty-four hours is not increased by exposing the dog to a temperature of 7.6°. The increased metabolism is entirely at the expense of fat. We have seen that this may also be true of work which may be accomplished at the expense of fat without raising the protein metabolism.

Reduced to terms of calories produced per kilogram of dog, the following results are obtained:

Temperature.	Calories per Kilo.
7.6°	86.4
15.0°	63.0
20.0°	55.9
25.0°	54.2
30.0°	56.2
35.0°	68.5

A temperature of 20° was readily borne by this dog without any increase of his metabolism. The period of unchanging metabolism extended over at least ten degrees between 20° and 30°, during which time the physical regulation alone sufficed to maintain evenly the body's temperature. At 35° a decided increase of heat production set in, on account of the warming of the cells through insufficient heat loss. That the range of the physical regulation of the temperature of this small dog was due to his long hair is shown by the change in his metabolism after shaving him. Rubner shows this in the following table:

Temperature.	Calories per Kilo.	
	Normal Coat of Hair.	Shaved.
20°	55.9	82.3
25°	54.2	61.2
30°	56.2	52.0

It is clearly seen that this dog lost his power of physical regulation between 20° and 30° as soon as he lost his covering of hair. His metabolism became like that of the guinea-pig, increasing with a reduction of temperature from 30° downward, an illustration of chemical regulation.

E. Voit[1] shows that the metabolism of a pigeon may be doubled after removing its feathers.

Babak[2] finds that if rabbits are shaved and varnished with starch paste their metabolism rises 140 per cent., which increase maintains their body temperature at the normal for several weeks, although the room temperature be between 15° and 20°.

To determine the influence of the second factor, that of the protecting layer of fat, Rubner[3] investigated the influence of temperature on the metabolism of a fasting short-haired dog at a time when he was emaciated, and compared it with the fasting metabolism after the same dog had been fattened. The results were as follows:

Dog (Thin).		Same Dog (Fat).	
Temperature.	Cal. per Kilo.	Temperature.	Cal. per Kilo.
5.1°	121.3	7.3°	120.5
14.4°	100.9	15.5°	83.0
23.3°	70.7	22.0°	67.0
30.6°	62.0	31.0°	64.5

It appears from the above that the metabolism of the dog was the same at a low temperature in both cases, but that the minimum metabolism was almost reached at a temperature of 22° when the dog had a protective covering of fat, which was not the case when he was thin. The presence of adipose tissue, therefore, acts in the same way as does a warm fur to extend the range of the physical regulation, and to delay the onset of the chemical regulation of body temperature.

The physical regulation may be increased by certain voluntary acts, such as are observed when a dog exposed to cold lies down and curls himself up in such a way as to offer as small an exposed surface as possible. The contrast to this is offered when on a hot day the dog lies on his back and extends his limbs so as to promote the loss of heat.

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[1] Voit: "Sitzungsber. der Ges. für Morph. u. Physiol.," 1904, xix, 39.

[2] Babák: "Pflüger's Archiv," 1905, cviii, 389.

[3] Rubner: *Loc. cit.*, 1902, p. 137.

Rubner[1] also cites an important modification of metabolism through a variation in the humidity of the atmosphere.

At a medium temperature during fasting (as well as on a medium diet) the metabolism of a dog was practically unaffected by an increase of humidity in the air, as appears below:

Temperature 20.2°	Calories in 24 Hours.	Humidity in Per Cent.
Dry day	258.4	34
Humid day	256.6	69
More on dry day	1.8	

However, on a liberal diet the metabolism increases on a damp day even at a medium temperature, as for example:

Temperature 20.2°	Calories in 24 Hours.	Humidity in Per Cent.
Very dry day	249.4	13
Humid day	261.9	66
More on humid day	12.5	

The increase is 5 per cent.

On a very hot day (on a moderate fat diet) the dog's metabolism is increased by the presence of moisture in the atmosphere.

Temperature 35°.

Calories per Kg.	Humidity in Per Cent.
69.28	9.1
73.54	30.0

Under these circumstances the metabolism rose 6.1 per cent. in the more humid air. There was probably an overwarming of the cells on account of the difficulty of heat loss by evaporation of water. A cold, damp environment of 0° to 5° temperature also favors an increased metabolism. Rubner attributes this action of humidity to the increased conductivity of a hair covering containing moisture, and says that this loss may be partially balanced by a decreased evaporation of water from the lungs.

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[1] Rubner: "Energiegesetze," 1902, p. 188.

Murschhauser and Hidding[1] have experimented with guinea-pigs' placed in various environmental temperatures and furnished either with perfectly dry air or air completely saturated with moisture. At 35° the well-known influence of air saturated with water increased the body temperature and, therefore, the metabolism. At both 20° and 5° the influence of cold was accentuated by excessive dryness of the air, so that the heat production was about 10 per cent. higher than in moist air at the same temperature. This is explained by the fact that in dry air evaporation of water from the lungs increased the loss of heat by the animal which was compensated for by an increased metabolism.

The metabolism and the manner of heat loss may, therefore, be variously affected by the condition of the atmosphere as regards moisture.

On days of ordinary dryness Rubner[2] calculates the following division of the heat loss in a starving dog under the influence of different temperatures:

INFLUENCE OF TEMPERATURE ON MANNER OF HEAT LOSS

Temperature.	Calories Lost by Conduction and Radiation.	Calories Lost by Evaporation of Water.	Total Calories of Metabolism.	Humidity in Per Cent.
7°	78.5	7.9	86.4	24
15°	55.3	7.7	63.0	34
20°	45.3	10.6	55.9	29
25°	41.0	13.2	54.2	19
30°	33.2	23.0	56.2	14

It is clear that at 7° only a little heat is lost by the evaporation of water and the greater part by conduction and radiation. As the surrounding air becomes warmer the power to lose heat by radiation and conduction diminishes, and the loss through the evaporation of water increases.

Rubner has charted this experiment after making allowances[3] for the varying moisture conditions. The chart is

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[1] Murschhauser and Hidding: "Biochemische Zeitschrift," 1912, xlii, 357.

[2] Rubner: "Energiegesetze," 1902, p. 193.

[3] Rubner: "Archiv für Hygiene," 1891, xi, 208.

reproduced in Fig. 11, and epitomizes the method of heat loss in a starving dog under the influence of varying temperatures.

The discussion of the metabolism has given a foundation for the understanding of the basic requirement of an organism. The minimum requirement for energy is seen to be present when the fasting organism is surrounded by an atmosphere having a temperature of 30° to 35°. This may be called the *basal metabolism*, the minimum of energy compatible with cell life. This basal metabolism is modified by temperature, by food, and by work, and it is an important factor to keep in mind (see p. 124).

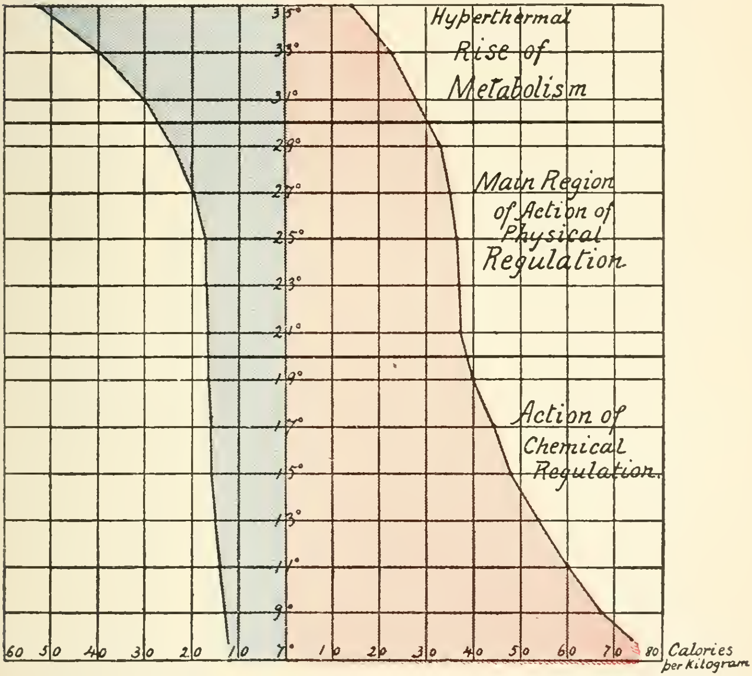

Fig. 11.—Rubner's chart showing the manner of heat loss at different room temperatures in the dog. *Blue*, Heat loss in calories through evaporation of water. *Red*, Heat loss in calories through radiation and conduction.

The distance between opposite points of the curved line represents the total metabolism at a particular temperature.

The principles laid down here regarding the lower animals apply equally to man. He too may come under the influence of chemical regulation, although he constantly endeavors to maintain the surface of his skin at a tropical temperature through the use of clothes. His heat loss may, like the dog's, be more difficult if he be covered with a thick layer of fat, and his metabolism is also influenced by atmospheric conditions of moisture, wind, and temperature.

One of the earliest demonstrations of the action of chemical regulation was afforded by Voit, who placed a fasting man weighing 70 kilograms in the Pettenkofer-Voit respiration apparatus and determined the carbon dioxid and nitrogen output for six hours. The person accustomed himself to the given temperature by staying under its influence for some time previous to the commencement of the experiment. In the cold experiments the ventilating air was derived from the winter atmosphere. For the warm periods the air was artificially heated. The subject of the experiment wore clothing which was comfortable in the usual warm atmosphere of the laboratory. Voit[1] gives the following results:

EFFECT OF TEMPERATURE ON THE METABOLISM OF A FASTING MAN. SIX-HOUR PERIODS

Temperature.	CO_2 Excreted in G.	N in Urine in G.
4.4°	210.7	4.23
6.5°	206.0	4.05
9.0°	192.0	4.20
14.3°	155.1	3.81
16.2°	158.3	4.00
23.7°	164.8	3.40
24.2°	166.5	3.34
26.7°	160.0	3.97
30.0°	170.6	

The nitrogen elimination remains unaffected by temperature. At the ordinary room temperature there scarcely seems to be any increase in carbon dioxid output, but at the lower temperatures the quantity of the fat metabolism is markedly increased, as shown by the rise of carbon dioxid

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[1] Voit: "Zeitschrift für Biologie," 1878, xiv, 80.

elimination. The individual sat quietly in a chair, but at a temperature of 4.4° C. could not prevent himself from shivering.

The whole effect of the chemical regulation in man has been attributed by Johansson[1] and also by Sjöström[2] to the additional metabolism due to shivering. Voit did not believe that this could be the cause, nor that the increased respiratory activity could account for the rise in metabolism. Voit believed the increase to be a reflex stimulus of cold on the skin which raised the power of the muscle cells to metabolize. Voit's views have been confirmed in Rubner's laboratory[3] in the following series of experiments on a man:

Temperature.	CO_2 in Grams per Hour.
15°	32.3
20°	30.0
23°	27.9
25°	31.7
29°	32.4

In this experiment there was no shivering at a temperature of 15°, and yet the metabolism increased from what it was at 23°.

It has also been shown that cool baths and winds increase the metabolism, which must be effected through the chemical regulation. Lefèvre[4] states that a man who has been inured to it may sit naked for several hours in a cold wind without a reduction of body temperature.

Rubner[5] has measured the effect of baths and douches lasting three and a half to five minutes. When the water has a temperature of 16° he finds that the carbon dioxid elimination may be very largely increased, especially in the case of the douche. The effect of the douche was more marked if taken before breakfast when the intestinal tract was free from food. The results before breakfast were as follows:

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[1] Johansson: "Skan. Archiv für Physiologie," 1897, vii, 123.
[2] Sjöström: "Skan. Archiv für Physiologie," 1913, xxx, 1.
[3] Rubner: "Energiegesetze," 1902, p. 203.
[4] Lefèvre: "Comptes rendus," 1894, p. 604.
[5] Rubner: "Archiv für Hygiene," 1903, xlvi, 390.

INFLUENCE OF COLD BATHS ON METABOLISM IN MAN

	Douche 16°. Increase in Per Cent.	Bath 16°. Increase in Per Cent.
Volume of respiration	54.5	22.9
Carbon dioxid excreted	149.5	64.8
Oxygen absorbed	110.1	46.8

A cold bath, especially a douche, will therefore stimulate to a greatly increased metabolism. The mechanical stimulus of the falling cold water apparently acts reflexly to increase the metabolism greatly, as it certainly does the magnitude of the respiration. The respiratory quotient indicates that the increased metabolism is at the expense of the glycogen supply. There is an after-effect which lasts about one and a half hours, indicating an increased metabolism during that time. This may be the expression of the body's attempt to maintain a normal temperature after being somewhat cooled (see also p. 322).

It is obvious that a cold bath will be likely to induce shivering unless by mechanical effort, such as swimming, the metabolism is increased so as to supply calorific energy in another way than through chemical regulation (see p. 312).

A bath of 35° has no effect on metabolism.

Rubner finds that a bath at 44° again increases the metabolism, the increase being, for the volume of respiration, 18.8 per cent., for carbon dioxid 32.1 per cent., and for oxygen 17.3 per cent. This is probably due to the overwarming of the cells. Baths at this temperature find favor among the Japanese.

Lusk[1] found that immersion before breakfast of men in baths at a temperature of 8° which contained cracked ice increased the heat production during a subsequent period of violent shivering to 180 per cent. above the normal. The metabolism was the equivalent of 4500 calories per day for a

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[1] Lusk: "American Journal of Physiology," 1910–11, xxvii, 427.

man weighing 64.7 kilograms. From the respiratory quotient of 0.85 which was found, it may be computed that approximately half of this energy was derived from carbohydrates and half from fat. It is known that cold tends to remove glycogen from the animal body (see p. 458), and it has been shown by Freund and Marchand[1] that a low environmental temperature increases the amount of sugar in the blood.

Schapals[2] brings confirmatory evidence as to the outcome of immersion of men in hot and cold baths:

	O_2 per Minute.	R. Q.	Increase in O_2 in Per Cent.
Normal	223.7	0.78	
Hot bath at 42°	274.0	1.09	15
Normal	278.7	0.78	
Cold bath at 17°	601.0	0.86	116

The higher respiratory quotients obtained may in part be due to a quickened respiration and consequent elimination from the blood of carbon dioxid not belonging to the metabolism of the period The German term "Auspumpung" properly defines this procedure. In metabolism work this possibility should be always sharply borne in mind.

The effect of wind is such that an imperceptible air current may have a very pronounced influence. Rubner[3] has shown that wind becomes perceptible when it attains a velocity of 0.4 to 0.5 meter a second, and that if a wind much below this *threshold* value, having a velocity of 0.18 meter per second, act upon the exposed area of the arm, there is an increased heat loss of between 19 and 75 per cent., depending on the temperature of the wind, above what would be lost were the air quiet.

The effect of wind of moderate humidity and different temperatures on the metabolism of a man clad in summer clothes, as compared with the metabolism during atmospheric calm, is shown in Wolpert's[4] experiment below:

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[1] Freund and Marchand: "Archiv für exp. Path. und Pharm.," 1913, lxxiii, 276.

[2] Schapals: "Zeitschrift für exp. Path. und Ther.," 1912, x, 222.

[3] Rubner: "Archiv für Hygiene," 1904, l, 296.

[4] Wolpert: "*Ibid.*, 1898, xxxiii, 206.

INFLUENCE OF WIND ON METABOLISM IN MAN.

Temperature.	Calm.	Wind 1 Meter per Second.	Wind 8 Meters per Second.
	Grams CO_2 per Hour.	Grams CO_2 per Hour.	Grams CO_2 per Hour.
2°	29.8		
10–15°	25.1	28.3	30.0
15–20°	24.1	....	30.1
20–25°	25.0	....	28.0
25–30°	25.3	22.2	24.4
30–35°	23.7	....	21.6
35–40°	21.2	22.2	22.1

According to this, a breeze having a temperature of 15° to 20° and moving at the rate of about 15 miles per hour (8 meters per second) has a greater effect upon the metabolism of a man clad in summer clothing than a temperature of 2° would have during perfect atmospheric quiet. In all the experiments the smallest amount of carbon dioxid is eliminated between 30° and 40°.

The above experiments were performed on a thin man, and it will be noticed that there was no rise in his metabolism at a temperature of between 35° and 40°. Rubner explains this as due to the sufficiency of the evaporation of perspiration on the surface for the cooling of the organism.

A fat man, however, with a thick, ill-conducting layer of adipose tissue is not so immune to the effect of high temperatures upon his metabolism. This is especially pronounced in a damp climate. Thus Rubner[1] obtains the following results from a fat man wearing clothes:

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[1] Rubner: "Energiegesetze," 1902, pp. 208, 232.

INFLUENCE OF TEMPERATURE AND HUMIDITY ON THE METABOLISM OF A FAT MAN

Temperature.	Humidity 30 Per Cent.		Humidity 60 Per Cent.	
	CO_2 in Grams per Hour.	H_2O Evaporated per Hour.	CO_2 in Grams per Hour.	H_2O evaporated per Hour.
20°	33.7	56	30.7	17
28–30°	36.9*	134	44.5‡	170+ 31 g. sweat.
36–37°	42.6†	204 +14 g. sweat.	46.7§	186 +255 g. sweat.

* Body temperature rose 0.1°.
† Body temperature rose 0.0°.
‡ Body temperature rose 0.4°.
§ Body temperature rose 0.9°.

The fact that in the experiment where there was 30 per cent. humidity the metabolism largely increased at 36° to 37° without concomitant rise in body temperature leads Rubner to theorize that there must have been an overheating of the cells where the metabolism was progressing, even though this might not have been determinable by the clinical thermometer.

It appears that on a hot, humid day the metabolism of a fat individual may be 50 per cent. higher than on a day of moderate temperature and the same humidity. The whole of the body heat is lost through the evaporation of water which is here hindered by the humidity. There is a large and exhausting excretion of sweat which on account of the difficulty in evaporation is not effective in cooling the body. At a moderate temperature, where the greater part of the heat loss is by radiation and conduction, the excretion of water is not excessive.

Lee[1] gives the following table which shows the influence of varying temperatures and humidities upon the body temperatures of a group of normal men:

Period of Confinement.	20° C. 50 Per Cent. Humidity.	23.9° C. 50 Per Cent. Humidity.	30° C. 80 Per Cent. Humidity.	30° C. 80 Per Cent. Humidity, with Fan Movement.
8.30 A. M.	37.12° C.	36.83° C.	36.86° C.	36.98° C.
3.30 P. M.	36.52° C.	37.02° C.	37.28° C.	37.37° C.

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[1] Lee: Proceedings of the Soc. for Ex. Biol. and Med., 1915, xii, 72.

There can be no doubt that climatic conditions modify racial characteristics. The emigrant from northern Europe, living upon a farm in the hot and often moist climate of an American summer, must restrict his layer of adipose tissue if he is to live comfortably. The same holds true in Italy. The difference between John Bull and Uncle Sam seems to be one of climatic adaptation. On the contrary, the Eskimo cultivates a thick, fat layer to protect himself from frost. It is also interesting to note that prostrations from the heat appear in New York with 66 per cent. humidity and a temperature of 31.5° (2.30 P. M., August 24, 1905). Rubner[1] says that a lightly clad thin man, at a temperature of 30° with humidity at 65 per cent., bore the effect so badly that he feared to raise the temperature to 35°. This individual had readily tolerated 35° in dry air.

The maximum mortality from "summer troubles" in children in New York coincides with the first great wave of heat accompanied by humidity which falls upon the city. Similar climatic conditions at later dates are not so fatal. It may be that the fatality of these intestinal affections is due to the inefficiency of the apparatus for the physical discharge of heat in the infant organism. It is also possible that infection may be more readily brought about under these conditions (p. 344).

Another factor in the heat regulation of man is clothes. Certain savage races living in cool climates do without clothes, as, for example, aborigines of Terra del Fuego, who, according to the reports of travelers, substituted a covering of oil. In such races the process of "hardening" or the development of the physical regulation must be carried to a maximum. In civilized countries man endeavors to remove all the influence of chemical regulation by keeping his skin covered. Only about 20 per cent. of his surface is normally exposed to the air. The most important constituent of clothes is the air, which is a much worse conductor of heat than is the fiber. This is especially true of furs (p. 136). Thickness of

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[1] Rubner: "Energiegesetze," 1902, p. 232.

the cloth will give a greater layer of air and will prevent heat loss from the body. A densely woven cloth prevents proper ventilation and does not absorb moisture. In hot weather a porous cloth next to the skin which can absorb moisture and permit its ready evaporation is of high importance. If a garment worn next to the skin becomes thoroughly wet the evaporation of sweat at a high temperature is largely prevented, to the great discomfort of the individual, while at a lower temperature heat loss through conduction is greatly facilitated, with a sensation of chill. Two experiments cited by Rubner[1] indicate the effect of clothes on metabolism. An individual was kept at a temperature of between 11° and 12° and wore different clothes at different times. His carbon dioxid and water excretion were as follows:

INFLUENCE OF CLOTHES ON METABOLISM IN MAN AT A TEMPERATURE OF 11° TO 12°.

	CO_2 in Grams per Hour.	H_2O in Grams per Hour.	Remarks.
Summer clothes	28.4	58	Cold, occasional shivering.
Summer clothes and winter overcoat	26.9	50	Chilly part of the time.
Summer clothes and fur coat	23.6	63	Comfortably warm.

When the man was comfortable the chemical regulation of temperature was eliminated.

Rubner remarks that while the radiant energy of the sun is large in quantity, he has been unable to find any influence upon a man under ordinary circumstances, but believes that it may take the place of heat produced through chemical regulation on cold days. Thus a person living in the high altitude of Davos, Switzerland, feels much more comfortable in the sun on a cold day than he does in the shade. However, Zuntz while living on the summit of Monte Rosa found that sunlight did not reduce metabolism (p. 429).

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[1] Rubner: "Energiegesetze," 1902, p. 225.

Hasselbalch[1] found that if the naked body of a man was strongly exposed to ultra-violet rays the rate of respiration was diminished while the depth was increased. The skin was red with dilated capillaries and the blood-pressure fell. Lindhard, in 1910, showed there is a yearly periodicity of the respiratory rate in the Arctic region, it being less in the spring and summer than in the winter. The enormous variations in the chemical intensity of the sun's rays in the Arctic region are undoubtedly the cause of this manifestation. Even in Copenhagen the same phenomenon has been observed by Hasselbalch and Lindhard.[2] The volume of respiration increases 26 per cent. in the summer. The intensity of the metabolic processes are not affected. This accords with the fact that there is no change in metabolism through an alteration of the respiratory rhythm induced by cutting the pulmonary branches of the vagus.[3]

Durig and Zuntz[4] find that the climate of the seashore does not influence the basal metabolism, nor does travel to the Canary Islands in the tropics,[5] nor the condition of sea-sickness.

The fundamental heat production in the organism is not reduced by liberating heat from electric energy within the organism.[6] Thus, although high frequency currents equal to 1.8 amperes and 176 volts were passed through the body during two and one-half hours under conditions such as avoided high concentration, and though heat was produced thereby which was equal to three to four times the energy requirement of the time, yet there was in fact a slight increase in the oxidative processes of the subjects attributable to hyperthermia, sweating, increased pulse, and respiratory activity.

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[1] Hasselbalch: "Skan. Archiv f. Physiol.," 1905, xvii, 431.

[2] Hasselbalch and Lindhard: "Skan. Arch. f. Physiol.," 1911, xxv, 361; *Ibid.*, 1912, xxvi, 221.

[3] Rauber and Voit: "Sitzungsber. der baeyerischen Akademie," 1868.

[4] Durig and Zuntz: "Biochemische Zeitschrift," 1912, xxxix, 422; *Ibid.*, p. 435.

[5] For an interesting discussion of the offects of tropical light on white men read C. E. Woodruff, "Medical Ethnology," New York, 1915.

[6] Durig and Grau: "Biochemische Zeitschrift," 1912–13, xlviii, 480.

Extraneous heat, therefore, will not replace the chemical energy of the food-stuffs in maintaining the life processes.

In what follows it will be shown that the ingestion of food may add to the heat production of the organism and diminish the necessity of heat production through chemical regulation in cold weather. Also it may very uncomfortably increase the production of heat and perspiration in warm weather, especially if protein be largely taken (p. 247).

From this chapter the influence of climate is seen to be noteworthy. It explains why a temperature of —40° may be comfortably borne in winter, in the Adirondack Mountains, for example, if the air be dry and still; why a much warmer atmosphere which is damp and windy may "cut to the bone" with cold; why a hot, dry climate may be entirely comfortable, when air at the same temperature laden with moisture may strike down many fatally and oppress every one; and how the effect of heat may be modified by the breezes and baths at the seashore. It does not explain the effect of the dry sirocco wind which blows from the Desert of Sahara, the universal depressant action of which has been attributed to unknown cosmic influences.

CHAPTER V

THE INFLUENCE OF PROTEIN FOOD

PART I—NITROGEN EQUILIBRIUM

It has been thought that protein is a food which is in itself sufficient for all the requirements of the body. Pflüger[1] was able to keep a very thin dog in good condition and doing active exercise during a period of seven months, the sole diet being meat cut as free from fat as possible. Pflüger says that the fat and glycogen content of the meat ingested could not have yielded sufficient energy to provide for the action of the heart alone. It must be remembered, however, that meat is not pure protein, but is mixed with salts and water. The simplest diet capable of maintaining the body in condition is, therefore, a mixture of materials or food-stuffs. Such a mixture of food-stuffs is called a food. A food-stuff is a material capable of being added to the body's substance, or one which when absorbed into the blood-stream will prevent or reduce the wasting of a necessary constituent of the organism.

The food-stuffs are:

Proteins (including albuminoids).
Carbohydrates.
Fats.
Salts.
Water.

A food is a palatable mixture of food-stuffs which is capable of maintaining the body in an equilibrium of substance, or capable of bringing it to a desired condition of substance. The ideal food is a palatable mixture of food-stuffs arranged

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[1] Pflüger: "Pflüger's Archiv," 1891, l, 98.

together in such proportion as to burden the organism with a minimum of labor. These definitions are Voit's.[1]

When protein alone is ingested by a normal adult it is very readily oxidized, and is only with the greatest difficulty deposited so as to form new tissue in the organism.

In the early experiments of Bischoff and Voit the fact is recorded that a dog weighing 35 kilograms may excrete 12 grams of urea in twenty-four hours, and the same dog after receiving 2500 grams of meat may excrete 184 grams, fifteen times as much.

Voit[2] has shown that if that quantity of meat be administered which corresponds to what is oxidized in starvation, nitrogen equilibrium will not be established, but some of the body's flesh will also be metabolized. This latter quantity grows steadily less if the amount of meat ingested be gradually increased until finally the point of *nitrogen equilibrium* is reached, at which the amount of meat ingested is equal to that destroyed in the body. To illustrate this Voit gives the following table, the results of work done on a dog:

Grams Meat Administered.	Grams Flesh Destroyed.	Change in the Body.
0	233	−233
0	190	−190
300	379	−79
600	665	−65
900	941	−41
1200	1180	+20
1500	1446	+54

Nitrogen equilibrium was not reached until 1200 grams of meat were given, or about five times the amount of the fasting protein metabolism.

The above experiments were made in 1858. It is no longer customary to calculate the protein metabolism in terms of flesh destroyed, but in terms of nitrogen. The old-fashioned term "flesh" meant meat with a nitrogen content of 3.4 per cent. It served to illuminate the significance of metabolism at a time when few were instructed in this field of work.

E. Voit and Korkunoff[3] have published a research of sim-

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[1] Voit: Hermann's Handbuch, "Stoffwechsel," 1881, pp. 330, 344.

[2] Voit: *Ibid.*, 1881, p. 106.

[3] E. Voit and Korkunoff: "Zeitschrift für Biologie," 1895, xxxii, 58.

ilar character. They fed a dog with meat which had been treated with lukewarm water to remove the extractives, and which was then squeezed in a press. This process removes most of the nitrogen-containing substances other than protein. A dog will readily eat this washed meat or "protein." The idea was to determine the minimum quantity of protein which it was possible to ingest and still maintain nitrogen equilibrium. The different quantities of meat tabulated below were given continuously for two or three days at a time. Only the results of the last day of each of these periods are quoted:

Food.	N in Food.	N in Excreta.	Difference.
Starvation	0	3.996	−3.996
100 gm. meat	4.10	5.558	−1.458
140 " "	5.74	6.495	−0.755
165 " "	6.77	7.217	−0.447
185 " "	7.59	7.804	−0.214
200 " "	8.20	8.726	−0.526
230 " "	10.24	10.579	−0.339
360 " "	11.99	12.052	−0.062
410 " "	15.58	14.314	+1.266
360 " "	13.68	13.622	+0.058
Starvation, third day		4.026	−4.026

The figures show that nitrogen equilibrium was reached only after supplying three and a half times the amount of protein metabolized in starvation. The authors calculate that at this time of nitrogen equilibrium the dog was still losing 28 grams of body fat, and that not much more than 50 per cent. of the total energy liberated in the organism was furnished by the protein metabolism of the time. *One may thus have nitrogen equilibrium without having carbon equilibrium.*

Systems of diet for fat people are based on this knowledge. A loss of protein is highly undesirable, while a gradual loss of adipose tissue may be a great relief to the obese.

Bornstein[1] finds that during a period of thirteen days he can add 8.3 grams of protein to his body and oxidize 90 grams of body fat daily when ingesting a mixed diet containing 1600 calories with 118 grams of protein. Such a diet contains a fuel value less than the requirement of his organism (p. 279).

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[1] Bornstein: "Berliner klinische Wochenschrift," 1904, xli, 1192.

This cannot be accomplished without carbohydrate in the diet, for Thomas[1] finds that when a man is given protein alone, administered in fractional portions every two hours even to the extent of double the quantity of protein destroyed in fasting, nitrogen equilibrium cannot be obtained. This experiment is given below; 500 grams of meat contained 18.4 grams of nitrogen, corresponding to about 115 grams of protein:

DAY	6	7	8	9	10	11	12	13	14	15
N in food	....	.....	8.63	8.63	8.63	15.54	17.27	18.39	18.40	18.39
N in urine	7.64	9.78	12.90	13.46	14.42	16.81	18.92	20.85	21.50	21.52
± N to body	−8.16	−10.00	−4.79	−4.79	−6.31	−1.79	−2.17	−2.97	−3.62	−3.64

If the quantity of meat ingested be steadily increased after nitrogenous equilibrium has been reached, the protein metabolism will gradually increase, nitrogenous equilibrium will be established at higher and higher levels, and there will be a corresponding diminution in the amount of fat burned. This was shown in 1862 in the following experiment of Voit,[2] who gave different quantities of meat to a large dog weighing 30 kilograms:

INFLUENCE OF INGESTING INCREASING QUANTITIES OF MEAT

Weights are in Grams

MEAT INGESTED.	FLESH DESTROYED.	GAIN OR LOSS OF BODY FLESH.	GAIN OR LOSS OF BODY FAT.	O_2	CO_2	R. Q.
0	165	−165	−95	330	327	.72
500	599	−99	−47	341	356	.76
1000	1079	−79	−19	453	463	.74
1500	1500	0	+4	487	547	.81
1800	1757	+43	+1	—	656	—
2000	2044	−44	+58	517	604	.84
2500	2512	−12	+57	—	783	—

Nitrogen equilibrium existed after the ingestion of 1500 grams of meat and there was also no loss of body fat (carbon equilibrium). When 2000 grams and even 2500 grams of

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[1] Thomas: "Archiv für Physiologie," 1910 Suppl., p. 249.
[2] Voit: "Stoffwechsel," 1881, p. 117.

meat were supplied it was all destroyed, as was indicated by the amount of nitrogen in the urine, but a certain quantity of carbon belonging to the ingested protein was not eliminated in the respiration, but was retained in the body. This carbon Pettenkofer and Voit believed to have been laid up in the body in the form of fat.

The respiratory quotient in the foregoing series gradually rises, as would be expected from the increasing prominence of the protein in the metabolism (p. 60). Meat alone will therefore support a dog. Rubner[1] says that a man cannot live on meat alone, not because the intestinal canal cannot digest it, but because of the physical limitations of the apparatus of mastication. A dog weighing 10 kilograms may ingest 1000 grams of chopped meat in forty-five seconds, while a man requires between five and ten minutes rapidly to cut and partake of 200 grams of good sirloin steak.

A subject of interest in considering the value of protein in metabolism is that of the value of gelatin. Gelatin is an artificial derivative of collagen, an albuminoid largely found in the skeletal structure of animals. Gelatin contains very nearly the same quantity of nitrogen as protein; it breaks up on chemical treatment into the same amino-acids, except that it does not yield tyrosin, cystin, and tryptophan. In the diabetic, gelatin yields the same amount of sugar as does protein.[2] To what extent gelatin may take the place of protein in the body's metabolism has long been the subject of inquiry.

It was shown first by Bischoff and Voit[3] that no matter how much gelatin was ingested, it was always completely burned, and some of the body's protein in addition. Therefore gelatin never builds up new tissue, although it may somewhat diminish tissue waste. Gelatin may be formed from protein in the body, but it cannot be reconverted into protein nor act like protein in metabolism. Kirchmann,[4] working

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[1] Rubner: von Leyden's "Handbuch der Ernährungstherapie," 1903, i, 42.
[2] Reilly, Nolan, and Lusk: "American Journal of Physiology," 1898, i, 395.
[3] Voit: Hermann's Handbuch, "Stoffwechsel," 1881, p. 396.
[4] Kirchmann: "Zeitschrift für Biologie," 1900, xl, 54.

in the laboratory of Erwin Voit, has shown to what extent gelatin spares protein in metabolism. If one takes the amount of protein metabolism in starvation as one, then the ingestion of about the same quantity of gelatin reduces the body's protein waste 23 per cent., and if eight times this amount of gelatin be given, the tissue waste may be reduced 35 per cent. In other words, the ingestion of 7.5 per cent. of the total heat requirement of the organism in the form of gelatin spares 23 per cent. of the body's protein, while the ingestion of 60 per cent. of the requirement will only cause a decrease of 35 per cent. in protein waste. Krummacher[1] showed that the ingestion of the full heat requirement of the animal in the form of gelatin reduced the fasting protein metabolism by only 37.5 per cent. It is evident that no matter how much gelatin be given, tissue protein continues to be destroyed, and it is also evident that a small quantity of gelatin has almost as great an effect as a large quantity.

An extremely interesting experiment of Kauffmann[2] shows that when the lacking tyrosin, cystin, and tryptophan are mixed with gelatin in the proportions in which they occur in true protein, and are given to a dog or to a man, nitrogen equilibrium may be established. Abderhalden[3] confirms this in similar experiments.

It is evident, therefore, that the value of the various proteins in nutrition may depend upon their constituent amino-acids, and this will be considered on another occasion (see p. 371).

It appears that protein bodies must be broken up into amino-acids before absorption in the intestine (p. 79). If this be true, then ingestion of the cleavage products of protein should maintain nitrogen equilibrium in the same way as the ingestion of meat. The first experiments in this direction were done by Loewi,[4] who gave a dog pancreas which had been

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[1] Krummacher: "Zeitschrift für Biologie," 1901, xlii, 242.

[2] Kauffmann: "Pflüger's Archiv," 1905, cix, 440.

[3] Abderhalden: "Zeitschrift für physiologische Chemie," 1912, lxxvii, 22.

[4] Loewi: "Archiv für ex. Path. und Pharm.," 1902, xlviii, 303.

self-digested until all the protein had been converted into amino-acids, as was indicated by the almost complete disappearance of the biuret reaction. Fat and carbohydrates were given with the digest, and nitrogen equilibrium was obtained and even nitrogen retention accomplished. Thus, in one experiment covering a period of eleven days, proteolytic digestive products containing an average of 6.08 grams of nitrogen were given daily, of which only 5.19 grams were eliminated in the excreta, while the balance, or 0.89 gram of nitrogen, was retained in the body of the animal. This amounted to 9.79 grams of nitrogen in eleven days. Accompanying this nitrogen retention was one of 0.649 gram of phosphoric acid (P_2O_5), an amount larger than was necessary for the upbuilding of new tissue from the nitrogen compounds retained. Loewi concluded that he had demonstrated the synthesis of new protein within the organism.

Henderson and Dean[1] confirmed Loewi by finding that they could obtain nitrogen equilibrium by feeding a dog with the cleavage products of meat produced by treatment with sulphuric acid.

Abderhalden and Rona[2] find that mice live on casein split with pancreatin as long as they do on casein alone; whereas they die much earlier if the casein has been submitted to peptic and then pancreatic digestion, or if it has been broken up by acid hydrolysis. Henriques and Hansen[3] also find that casein broken up by acid will not maintain nitrogen equilibrium in rats, but that if the pancreas of the ox and a small piece of the intestine of the dog (to furnish erepsin) be digested for two months at 40°, and the resulting material given to rats, nitrogen equilibrium will be maintained. The authors further find that the mono-amino-acid fraction (the filtrate after precipitation with phosphowolframic acid) and also the alcoholic extract of the last-named digest maintain rats in

[1] Henderson and Dean: "American Journal of Physiology," 1903, ix, 386.

[2] Abderhalden and Rona: "Zeitschrift für physiologische Chemie," 1904, xlii, 528.

[3] Henriques and Hansen: *Ibid.*, 1905, xliii, 417.

nitrogen equilibrium. The residue left after alcoholic extraction will not do so.

Abderhalden and Rona[1] have accomplished a most interesting experiment upon a dog. The animal was given daily a constant quantity of non-nitrogenous foods which were: fat, 25 grams; starch, 50 grams; cane-sugar, 10 grams; glucose, 5 grams. The dog was brought into nitrogen equilibrium by giving him meat containing 2 grams of nitrogen. Then for this were substituted the amino cleavage products of casein, produced by pancreatic digestion and also containing 2 grams of nitrogen. During sixteen days on this diet there was an average daily gain of 0.12 gram of nitrogen by the dog. Then casein hydrolized by acid and containing 2 grams of nitrogen was administered for ten days, during which time the dog lost 0.48 gram of nitrogen daily. Amino products prepared after this fashion will, therefore, not preserve nitrogen equilibrium. Lastly, the diet was continued without any nitrogenous food. The daily waste of body nitrogen was then 0.53 gram. The loss was the same as when the casein hydrolized by acid was ingested, indicating that this particular array of cleavage products had no protecting power over the body protein.

Henriques[2] has hydrolized protein by digesting it with trypsin and erepsin and then treating with 20 per cent. sulphuric acid on the water-bath. The resulting material consists entirely of amino-acids with no admixture of polypeptids, and if it still gives a pronounced tryptophan reaction it will support the organism in nitrogen equilibrium. *In the absence of the single amino-acid tryptophan, nitrogen equilibrium cannot be attained.*

To complete the story, the work of Abderhalden[3] must be recited. Nitrogen equilibrium and even nitrogen retention were established in a dog when the diet contained instead of protein the following mixture of pure amino-acids: Glycocoll

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[1] Abderhalden and Rona: "Zeitschrift für physiologische Chemie," 1905, xliv, 198.

[2] Henriques: *Ibid.*, 1907, liv, 406.

[3] Abderhalden: "Zeitschr. f. physiol. Chem.," 1912, lxxvii, 22.

5 grams, d-alanin 10 grams, l-serin 3 grams, l-cystin 2 grams, d-valin 5 grams, l-leucin 10 grams, d-isoleucin 5 grams, l-aspartic acid 5 grams, d-glutamic acid 15 grams, l-phenylalanin 5 grams, l-tyrosin 5 grams, l-lysin 5 grams, d-arginin 5 grams, l-prolin 10 grams, l-histidin 5 grams, and l-tryptophan 5 grams. This mixture weighed 100 grams and contained 13.87 grams of nitrogen. It is not unlike ox muscle in relative composition (see p. 77).

It is therefore proved that amino bodies resulting from certain proteolytic cleavages may be the equivalent in metabolism of ingested protein itself.

In practical dietetics these substances can have little value, as they tend to produce diarrhea, as do also albumoses and peptones when given in any considerable quantity.[1] As illustrating this Cronheim[2] finds that though "Somatose" is more digestible than meat, still over 30 grams are undesirable in the daily diet of a man.

It is certain that if there be a new construction of protein in the body from the amino-acids formed in digestion such new proteins are characteristic of the organism, and do not possess the properties of the proteins originally ingested. To illustrate this Abderhalden and Samuely[3] gave to a horse 1500 grams of gliadin, a vegetable protein which contains 36.5 per cent. of glutamic acid. They wondered if the ingestion of such a protein would in any way modify the composition of the proteins of the blood-serum, of serum globulin which under ordinary circumstances contains 8.5 per cent., and of serum albumin which contains 7.7 per cent. of glutamic acid. Their results were as follows:

INFLUENCE OF GLIADIN INGESTION ON THE PERCENTAGE OF GLUTAMIC ACID IN THE SERUM PROTEINS OF THE HORSE

Experiment.	Normal Day.	After Fasting 7 or 8 Days.	After Ingesting 1500 G. Gliadin.	
			Day 1.	Day 2.
I	8.85	8.20	7.88	8.25
II	9.52	8.52	8.00	

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[1] Voit, F.: "Münchener med. Wochenschrift," 1899, xlvi, 172.

[2] Cronheim: "Pflüger's Archiv," 1904, cvi, 17.

[3] Abderhalden and Samuely: "Zeitschrift für physiologische Chemie," 1905, xlvi, 193.

It is evident that gliadin, which contains so large a proportion of glutamic acid, is without influence on the composition of the blood-serum. Abderhalden conceived that such proportions of the amino-acids within the gliadin complex as are available for the formation of new serum albumin and serum globulin were used for the generation of these proteins. Evidence that amino-acids enter the blood-stream directly from the intestinal tract has already been submitted. Furthermore, Henriques and Anderson[1] have administered continuous intravenous injections of meat hydrolized with trypsin and erepsin to goats which had survived the operation of extirpating the intestines, and have noted nitrogen retention. From this they conclude that the intestine is not necessary for protein regeneration.

It has already been stated (p. 74) that if the serum of a dog be injected into the blood-vessels of another dog the nitrogen of it will be eliminated in the urine. This is also true of proteins foreign to the organism, and these likewise act in a toxic manner to destroy body protein. Thus Mendel and Rockwood[2] have shown that if edestin, a pure crystalline protein prepared from hemp seed, be injected intravenously into a fasting dog, there is for two days a metabolism of protein which is much greater than that of former days plus that of the edestin administered. The same truth holds when casein is injected. Similar injection of horses' serum into dogs appears to have no toxic action (Rona and Michaelis[3]). This work is of interest in connection with the subject of *anaphylaxis*, called also the Theobald Smith phenomenon, which has been especially investigated by Rosenau and Anderson. Injections of a protein foreign to the organism render the body sensitive to a second injection of the same protein. Large or small amounts of foreign protein may be injected in the

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[1] Henriques and Anderson: "Zeitschrift für physiologische Chemie," 1914, xcii, 194.

[2] Mendel and Rockwood: "American Journal of Physiology," 1904, xii, 350.

[3] Rona and Michaelis: "Pflüger's Archiv," 1908, cxxi, 163; 1908, cxxiii, 406.

first instance without intoxication, but if the animal be once "sensitized" a small amount of the same protein will terminate the animal's existence. It has recently been stated by Wells[1] that the injection of so minimal an amount as $\frac{1}{1000000}$ gram of pure crystalline egg-albumin will "sensitize" a guinea-pig so that a subsequent injection into the blood of $\frac{1}{10}$ milligram of the same substance is lethal, although such a dose given in the first instance would not have injured the animal. It is evident, therefore, that the alimentary canal cannot allow the passage of proteins without changing them. This also explains the complete immunity of the organism to snake venom which has been swallowed.

The effect of copious drinking of water upon protein metabolism has been made the subject of various studies. A small increase in nitrogen elimination has usually been noted. This was first established by Voit, who explained it as due to an increased circulation which influenced the flow of the intracellular fluids. Heilner[2] has shown that giving 2000 c.c. of water to a fasting dog on two successive days raises his urinary nitrogen from 3.15 grams to 4.09 and 3.58 grams on the two days of water ingestion, and then the nitrogen excretion falls to 2.22 and 2.62 on the following days. In this experiment the carbon dioxid excretion was very slightly increased and the temperature of the dog was not affected. The quantity of urine rose from 90 to 2050 c.c.

Straub[3] found that an extra ingestion of 2000 c.c. of water in a man who was in nitrogen equilibrium on a diet containing 20.56 grams of nitrogen had no effect on protein metabolism; whereas Hawk,[4] who gave less protein nitrogen but more water, found that the ingestion of 4500 c.c. of water caused the urinary nitrogen to rise from 11.03 to 12.48 on the first day, and 11.82 on the second day, with a fall to 10.91 grams on the suc-

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[1] Wells: Proceedings of the Society for Experimental Biology and Medicine, 1908, vi, 1.

[2] Heilner: "Zeitschrift für Biologie," 1906, xlvii, 541.

[3] Straub: *Ibid.*, 1899, xxxvii, 527.

[4] Hawk: "University of Pennsylvania Medical Bulletin," March, 1905.

ceeding day when no water was given. Hawk interprets the action of copious water drinking as twofold: *first*, to cause a removal of any accumulation of nitrogenous decomposition products from the organism, as was indicated by the greater increase of 12.8 per cent. in the nitrogen elimination of the first day; and, *second*, to cause a true increase in protein metabolism, as was indicated by the smaller increase of 6.8 per cent. on the second day of water ingestion.

Abderhalden and Bloch[1] have given a fixed diet to a person suffering from alkaptonuria (see p. 178) and on one of the days of the experiment have caused him to ingest 5 liters of water. The results of their analyses gave the following figures:

	N Balance.	N in Urine.	Homogentisic Acid.
Normal Food............	+1.36	18.2	10.52
" " + 5 L. Water	**−2.19**	**21.75**	**10.18**
" "	+1.47	18.09	10.27

Abderhalden believes that the constancy of the output of homogentisic acid indicates a constancy of protein metabolism throughout, whereas the rise in total nitrogen elimination in the urine represents a washing out of the nitrogenous end-products as a result of the large ingestion of water.

One of the striking characteristics of starvation metabolism was shown to be its extreme regularity from hour to hour and from day to day. What, then, is the hour-to-hour metabolism after meat ingestion?

The classical experiments of Voit[2] and of Feder[3] have been more fully worked over by Gruber. Gruber[4] fed a dog with 500, 1000, and 1500 grams of meat on different days. He collected the urine every two hours after the meal and determined the nitrogen output. The curves of nitrogen elimination under these circumstances are as follows:

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[1] Abderhalden and Bloch: "Zeitschrift für physiologische Chemie," 1907, liii, 464.

[2] Voit: "Physiologische Untersuchungen," Augsburg, 1857, p. 42.

[3] Feder: "Zeitschrift für Biologie," 1881, xvii, 541.

[4] Gruber: *Ibid.*, 1901, xlii, 421.

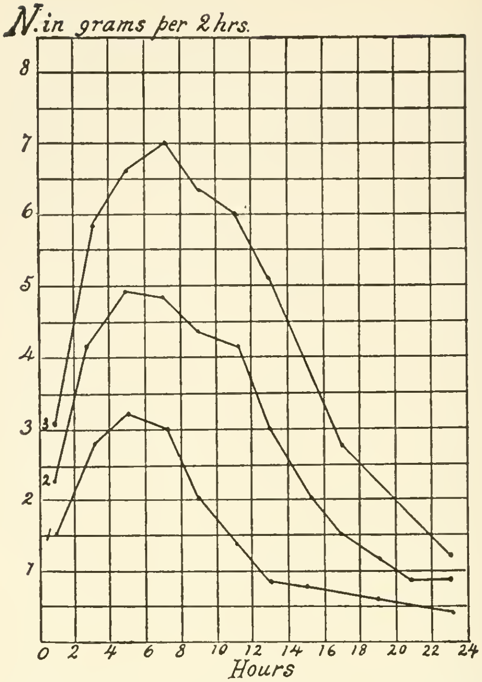

Fig. 12.—1, After 500 g. meat + 50 g. fat + 350 c.c. water; 2, after 1000 g. meat + 200 c.c. water; 3, after 1500 g. meat + 500 c.c. water. On each of these days the animal was in nitrogen equilibrium.

It is evident that there is an early elimination of protein nitrogen which here reaches a maximum between five and seven hours after feeding, and that the hour of the maximum excretion is delayed by increasing the quantity of meat ingested.

It is apparent, therefore, that the protein metabolism as illustrated by the curve of nitrogen elimination is quite different from its even metabolism in starvation.

Haas[1] in experiments on man finds that the curve of nitrogen elimination after a breakfast consisting of milk, bread, butter, and cheese always shows two maxima, the first in the second hour and the second in the fifth. The first rise in the curve is due to the removal of nitrogenous end-products already

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[1] Haas: "Biochemische Zeitschrift," 1908, xii, 203.

in the system and is caused by the early absorption of liquids taken with the food. The second rise corresponds to the absorption of food protein. Haas believes this to be the true explanation, because if diuresis be first induced by drinking tea, with a consequent washing out of urea from the body, then partaking of breakfast no longer causes so high a primary rise of nitrogen elimination, nor is the total elimination so great as in the experiments without preliminary diuresis. The experiment shows that for short periods the nitrogen excretion is not a true index of urea production. Severe muscular work has no influence upon the character of the curve described except when the quantity of urine produced is diminished, in which case the urea elimination is also reduced.

Confirming Albarran,[1] Barringer and Barringer[2] note that the volumes and the nitrogen content of the urine from the two kidneys are almost identical.

Urea in the organism undergoes no chemical change; there is no reversible reaction in the sense of ammonia formation.[3] When urea is retained in the body it is found widely distributed in all the tissues excepting fatty tissue; if it be administered intravenously to a dog diffusion to all parts of the body is complete in a few minutes.[4] A concentration of 1.2 per cent. may sometimes be reached in the dog, though one of over 1 per cent. is usually fatal.

The amount of urea excretion is found to be closely parallel to the urea concentration of the blood. This relation was formulated in Ambard's laws of urea elimination.[5]

(1) When the concentration of urea in the urine is constant the quantity of urea excreted in the urine varies proportionately to the square of the concentration of urea in the blood.

(2) When the concentration of urea in the blood remains

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[1] Albarran: "Exploration des fonctions rénales," Paris, 1905, p. 329.

[2] Barringer and Barringer: "Amer. Jour. of Physiology," 1910–11, xxvii, 119.

[3] Janney: "Zeitschrift für physiologische Chemie," 1911–12, lxxvi, 99.

[4] Marshall and Davis: "Journal of Biological Chemistry," 1914, xviii, 53.

[5] Ambard: "Comptes rendus société de biologie," 1910, lxii, 506.

constant the quantity excreted in the urine varies inversely as the square root of the concentration in the urine.

From these laws Ambard's coefficient or constant for the urea elimination through the kidney of human subjects was evolved. Arbitrary standards of normal weight, such as 70 kilograms, and of urea excreted in twenty-four hours, such as 25 grams, were adopted in the formula, which is as follows:

$$\frac{\mathrm{Ur}}{\sqrt{\mathrm{D} \times \frac{70}{\mathrm{Wt}} \times \sqrt{\frac{\mathrm{C}}{25}}}} = \text{K or Constant of Ambard.}$$

Ur = Urea per liter of blood in grams.
D = Urea in urine in twenty-four hours in grams.
Wt = Weight of patient in kilograms.
C = Concentration, or grams urea per liter of urine.

Ambard found the constant in normal individuals varied between 0.06 and 0.07. McLean,[1] who has used more accurate methods for measuring urea, finds the constant to be nearer 0.08, with wider variations than French observers found. This coefficient is being applied to determine kidney efficiency in renal disease. When the coefficient is found to be much increased, then urea is being retained by the organism on account of renal insufficiency.

Citing from McLean and Selling,[2] the following results may be given:

Person.	Time.	Urea N			Ambard's Coefficient.
		In Blood.	In Urine.		
			In 24 Hours.	Per Liter.	
		Mg.	Grams.	Grams.	
F. C. M.	Forty-five minutes after 10 g. urea	24	24.6	16.4	0.068
F. C. M.	Three days low protein diet	14	6.9	9.7	0.085
H. K. A.	After heavy dinner	22	11.4	11.6	0.088
B.	Nephritic	29	9.6	7.6	0.150

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[1] McLean: "Journal of Exp. Medicine," 1915, xxii, 212.

[2] McLean and Selling: "Journal of Biological Chemistry," 1914, xix, 31.

In some interesting work Pepper and Austin[1] find that after giving 900 grams of meat to a dog the non-protein nitrogen in the blood rises rapidly from 20 to 60 mg. per 100 c.c., and the urinary nitrogen rises from 0.15 gram to 1.1 grams per hour.

It is evident from this analysis that the curve of nitrogen elimination is not an exact indicator of the time relations of the breaking up of amino-acids in the body, for a part of the urea formed accumulates in the blood and is not at first eliminated in the urine, and too low a protein metabolism may thus in error be computed. Later, with a diminished absorption of amino-acids and diminished production of urea, the excess which is not attributable to the metabolism of the moment is eliminated from the blood, and the urinary nitrogen of these hours will give too high figures if used to compute the protein metabolism of short periods (see p. 173).

It may here be noted that the elimination of sodium chlorid follows Ambard's laws in the behavior of that quantity which is in excess of 5.62 grams of NaCl per liter of blood-plasma[2] (see p. 523) which is the threshold value of elimination by the kidney.

It was shown by Rubner,[3] who gave washed meat containing 24.72 grams of nitrogen to a dog daily for three days, that the sulphur elimination preceded that of the nitrogen, while that of phosphorus followed it. The results of the third day, at a time when the dog was essentially in nitrogen equilibrium, are divided into six hourly periods and are given below:

Period.	S.	N.	$\frac{N}{S}$	Of 100 Per Cent. were Excreted		
				S.	N.	P.
I.	0.448	5.57	12.4	**36.7**	24.8	16.0
II.	0.387	8.94	23.1	31.7	**39.8**	32.1
III.	0.257	5.32	20.7	21.1	23.6	**33.4**
IV.	0.131	2.66	20.3	10.5	11.8	18.5
	1.223	22.49	18.4			

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[1] Pepper and Austin: "Journal of Biological Chemistry," 1915, xxii, 81.
[2] For discussion, see McLean, *loc. cit.*
[3] Rubner: "Gesetze des Energieverbrauchs," 1902, 368.

The elimination of sulphur more rapidly than nitrogen after meat ingestion has been confirmed by von Wendt[1] in man. It appears that the end-products of the metabolism of sulphur-containing cystin appear in the urine more rapidly than urea, while phosphorus, which is an end-product of nuclein metabolism, makes its appearance more slowly.

Two explanations of the early elimination offer themselves: one, that the sulphur-containing cystin radicle is oxidized with exceptional ease; two, that the sulphur compounds may not accumulate in the organism as does urea. Variations in the rate of sulphur elimination may also undoubtedly be influenced by bacterial activity.

If in man various proteins be added to an already sufficient mixed diet (superposition experiments), the rate of destruction of the added protein as indicated by the extra N eliminated in the urine varies with the character of the protein. Such experiments were first devised by Falta,[2] who established the following classification of proteins in the order of the rapidity of their destruction: *a*, gelatin, casein, serum albumin, fibrin; *b*, blood globulin; *c*, hemoglobin; *d*, egg-albumin. Hämäläinen and Helme[3] continued these experiments and they also investigated the elimination of sulphur and phosphorus. They gave a man weighing 66 kilograms a diet containing 3650 calories and 5 grams of nitrogen. On this diet they superimposed on different days the following amounts of proteins:

800 g. white of egg = 14.40 g. N + 1.56 g. S.
57 g. proton = 6.94 g. N + 0.419 g. S.
320 g. veal = 13.44 g. N + 0.832 g. S.

and noticed the time of the elimination of nitrogen, sulphur, and phosphorus through the kidney. It was six days before all the nitrogen of the ingested white of egg was eliminated, whereas that in veal and proton required only two or three days. This is evident from the following table:

[1] von Wendt: "Skan. Archiv für Physiologie," 1905, xvii, 211.

[2] Falta: "Deutsches Archiv für klinische Medizin," 1906, lxxxvi, 517.

[3] Hämäläinen and Helme: "Skan. Archiv für Physiologie," 1907, xix, 182.

DAILY PERCENTAGE ELIMINATION OF THE NITROGEN, SULPHUR, AND PHOSPHORUS OF INGESTED PROTEIN SUPERIMPOSED ON AN ADEQUATE DIET

Day.	Egg-white.		Proton.		Veal.		
	N.	S.	N.	S.	N.	S.	P.
1	21	41.4	64	90	56	74.2	60
2	21	32.2	10	10	26	17.8	24
3	22	14.4	13	..	18	8.0	16
4	11	4.3	13				
5	14	5.5					
6	11	2.4					

The rapidity of the sulphur elimination is everywhere noticeable. The "nitrogen lag" in the case of white of egg is pronounced and may be due to the retention of peptids which are only slowly metabolized, or it may be due to the retention of amino-acids themselves.

Mendel and Lewis[1] suggest that the flattened curves of nitrogen elimination found after the ingestion of egg-white or ovalbumin may, to a great extent, be explained by a difference in the rate and completeness of the absorption of these substances when contrasted with the behavior of meat, casein, ovovitellin, edestin, gliadin and gelatin, between which little difference could be observed.

Cathcart and Green[2] have superimposed egg-albumin upon a vegetarian diet in man. In egg-albumin the ratio S : N is 1 : 8. The S : N of the urine in starvation is 1 : 15, but after ingesting egg-albumin it was found to be 1 : 9.8. This indicates a high specific oxidation of sulphur, and leaves a residuum of amino-acids suitable for regrouping into a pabulum of "deposit protein" which is poor in sulphur. It remains to be shown, however, whether such "deposit protein" if metabolized during the early days of fasting will give indication of a low sulphur content.

[1] Mendel and Lewis: "Journal of Biological Chemistry," 1913–14, xvi, 75.

[2] Cathcart and Green: "Biochemical Journal," 1913, vii, 1.

Sherman and Hawk[1] give curves showing beautifully an almost parallel elimination of sulphur and nitrogen in man on a mixed diet. A curve showing this is here presented:

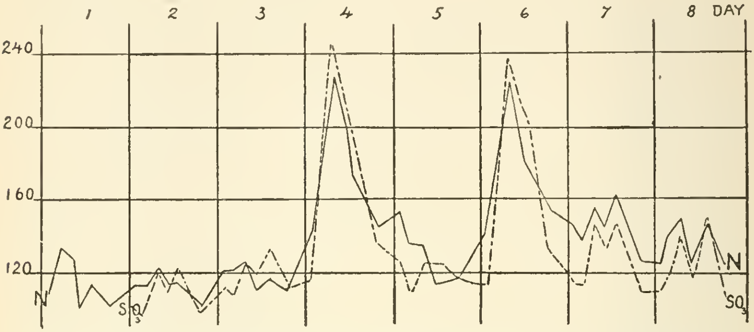

Fig. 13.—The curves here shown represent the relative fluctuations in the average rates of excretion of nitrogen and SO_3. The values on the left represent percentages of an assumed standard rate of excretion for each of these constituents. It will be seen that in general the excretion of sulphates ran quite closely parallel to that of nitrogen.

Wolf[2] presents similar curves after giving veal cutlets or casein to a man. It is evident that the early elimination of sulphur does not always appear. Wolf also describes experiments in which after the ingestion of a liter of raw white of egg by a man the maximal elimination of urinary sulphur followed that of urea by several hours. In this instance the ingesta contained 16.6 grams of nitrogen, and the urine during twenty-four hours only 8.7 grams. This indicates that a large fraction of the protein had a fate which is purely speculative.

If we pass from the consideration of protein metabolism, as indicated by the nitrogen curve, to the consideration of the intermediary metabolism of protein we can see more clearly that the curve of protein nitrogen excretion is not a true index to the sum of the activities contributed to the cells by protein metabolism.

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[1] Sherman and Hawk: "Amer. Jour. of Physiology," 1900, iv, 43.
[2] Wolf: "Biochemische Zeitschrift," 1912, xl, 193, 234.

CHAPTER VI

THE INFLUENCE OF PROTEIN FOOD (Continued)

PART II—THE INTERMEDIARY METABOLISM

THE term "intermediary metabolism" with which so much modern work is intimately associated was used by Bidder and Schmidt on the first page of their celebrated "Verdauungssäfte und Stoffwechsel," published in 1852. Their conception of the breakdown of protein has already been cited.

Voit[1] believed that there was an early cleavage of the protein molecule into a nitrogenous portion and a non-nitrogenous portion, a cleavage involving the liberation of only a small amount of energy; that there was a rapid combustion of the nitrogenous radicle, as shown by the elimination of the nitrogenous end-products in the urine; and that the non-nitrogenous radicle which contained the major part of the potential energy of the protein molecule might in part be temporatily stored either as glycogen or fat and be gradually doled out to the tissues as the need required.

Claude Bernard believed that glycogen could arise from protein. Wolffberg[2] let fowls fast two days to remove the glycogen and then for two days gave meat powder which was free from carbohydrate. Two fowls, killed during the interval of protein digestion, showed considerable glycogen in their livers (1.56 and 1.45 per cent.) and muscles (0.251 and 0.454 per cent.), much more than would have been present in starvation. Two similar fowls, killed seventeen and twenty-four hours after the last protein ingestion, contained much less glycogen in their livers (0.145 and 0.22 per cent.) and muscles (0.211 and 0.162 per cent.). This origin of glycogen from protein was fully confirmed by Külz[3] in a very extended series of

[1] Voit: "Zeitschrift für Biologie," 1891, xxviii, 291.
[2] Wolffberg: *Ibid.*, 1876, xii, 278.
[3] Külz: "Ludwig's Festschrift," 1890, p. 83.

experiments in which chopped meat, fully extracted with warm water, was made the basis of the ingesta. It became evident from these experiments that if sufficient protein were given to an animal, part of the protein carbon could be retained as glycogen.

It has long been believed that sugar arises from protein in diabetes. Kossel,[1] who knew that hexone bases, leucin, and other protein end-products contained six atoms of carbon, first suggested a relation between them and glucose. The theory of the origin of sugar in diabetes from these amino products was strongly advocated by Friedrich Müller.[2] The definite proof of this was afforded by Stiles and Lusk,[3] who gave a mixture of amino bodies prepared by the pancreatic proteolysis of meat to a dog rendered diabetic with phlorhizin. The mixture was free from protein. The nitrogen ingested was entirely eliminated in the urine, and for each gram of such nitrogen 2.4 grams of extra sugar appeared in the urine.

Considerable sugar may originate from protein in the course of its ordinary metabolism. The question arises at what time during the metabolism does this sugar become available for combustion in the organism? This question was answered by an experiment of Reilly, Nolan, and Lusk.[4] These authors gave a fasting phlorhizinized dog 500 grams of meat and collected the urine in two three-hour and one six-hour periods. The results were as follows:

EXCRETION OF GLUCOSE AND NITROGEN BEFORE AND AFTER INGESTING 500 GRAMS OF MEAT IN DIABETES

	Glucose.	Nitrogen.	D : N.
Preceding three hours	5.96	1.75	3.41
First three hours after feeding	12.43	2.52	4.92
Second three hours after feeding	14.70	3.76	3.91
Third three hours after feeding	11.23	3.85	2.92
Fourth three hours after feeding	11.23	3.85	2.92
Following three hours	6.34	1.78	3.56

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[1] Kossel: "Deutsche medizinische Wochenschrift," 1898, xxiv, 581.

[2] Müller and Seemann: *Ibid.*, 1899, xxv, 209.

[3] Stiles and Lusk: "American Journal of Physiology," 1903, ix, 380.

[4] Reilly, Nolan, and Lusk: "American Journal of Physiology," 1898, i, 395. For similar work after giving casein, serum albumin, gliadin, and edestin with separation of urine in hourly periods, consult Janney: "Journal of Biological Chemistry," 1915, xx, 321.

The normal fasting relation between glucose and nitrogen changed immediately upon the ingestion of meat. During the first hours more glucose was eliminated than corresponded to the nitrogen in the urine. During the later hours this proportion was reversed. The sugar elimination, therefore, took place decidedly before that of the nitrogen. This is shown in the following calculation of the percentage elimination of nitrogen and glucose in three-hour periods following the ingestion of 500 grams of meat in the above experiment:

	Glucose.	Nitrogen.
During first three hours	25.06	18.02
During second three hours	29.64	26.90
During third three hours	22.65	27.54
During fourth three hours	22.65	27.54
	100.00	100.00

The relations are represented in the following curve:

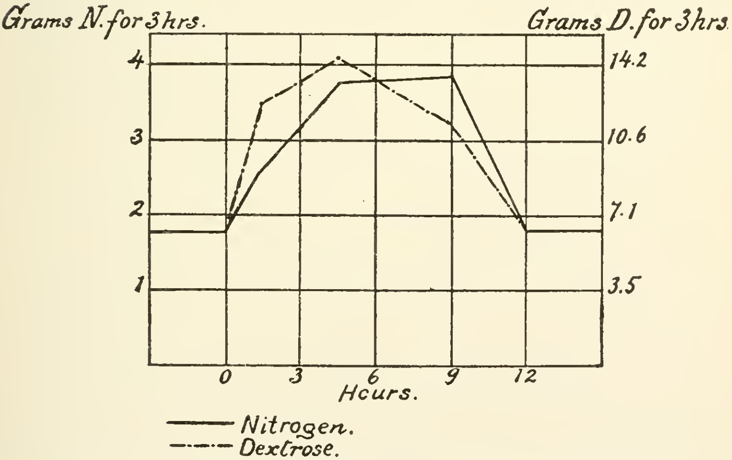

Fig. 14.—Curve showing the elimination of glucose before nitrogen after meat ingestion (500 grams) in diabetes.

That the glucose production from the meat ingested was proportional to the protein destroyed is evident from the following comparison, in which the sum of the glucose and nitrogen eliminated in the twelve hours is considered. Nitrogen and glucose double in quantity after the ingestion of meat, but their ratio remains the same as in starvation.

	Glucose.	Nitrogen.	D : N.
Fasting twelve hours	23.87	7.00	3.41
After 500 gm. meat, twelve hours	49.59	14.00	3.54
Subsequent twelve hours	25.36	7.11	3.56

The curve shows that there is an early production of sugar from protein which may be liberated in metabolism before the nitrogen belonging to the protein is eliminated in the urine. A similar early production of sugar from protein has also been observed after feeding dogs with meat in pancreas diabetes.[1]

Since 1 gram of nitrogen in the urine represents a destruction of 6.25 grams of meat protein, and since there is simultaneously an average elimination of 3.65 grams of glucose in phlorhizin diabetes, it may be calculated that the sugar production from meat amounts to 58 per cent. by weight of the meat protein metabolized and may contain 51 per cent. of its total available energy (see p. 471).

Another calculation shows that of the carbon from protein which is ordinarily eliminated in the respiration 57.2 per cent. may pass through the glucose stage (see p. 470).

After the ingestion of protein in the normal organism this sugar early becomes available and may be oxidized before the nitrogen belonging to it is eliminated, or if the sugar be formed in excess, it may be stored as glycogen in the liver and muscles of the body for subsequent use. In this way it is obvious that at least half the energy in protein may be independent of the curve of nitrogen elimination, but may rather act as though it had been ingested in the form of carbohydrate. This will be explained in the next chapter. It is therefore evident that this carbohydrate, which is early supplied in the breaking down of protein, may distribute its energy according to the requirement of the cells as long as it lasts. This is apparently the principal cause of the comparative evenness of the carbon

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[1] Berger: Inaugural Dissertation, Halle (Nebelthau), 1901; cited from Maly's "Jahresbericht über Thierchemie," xxxi, 848.

dioxid excretion as contrasted with the great irregularity of the nitrogen elimination after protein ingestion.

Pflüger who, longer than any physiologist, denied the validity of any existing proof that glucose arose from protein, was in his old age ultimately convinced by the following experiments. He[1] found that when dogs were allowed to fast for ten days and then made diabetic by an injection of phlorhizin the glycogen of the liver amounted to 0.1 per cent. and of the muscles to 0.2 per cent. If dogs reduced to this condition were given large quantities of codfish (which contains only 0.03 per cent. glycogen) the glycogen content of the liver averaged 6.5 per cent., and in one case rose to 9.9 per cent., and the glycogen content of the muscle averaged 1 per cent. Since fat ingestion was without effect upon the glycogen store, Pflüger acknowledged the origin of glucose from protein.

It must be borne in mind that it is not very long ago that it was perfectly permissible to think of protein as a complex containing many glucose molecules existing in a highly polymerized condition and combined with nitrogen-containing radicles, of which glycocoll, leucin, and tyrosin at least were readily obtainable as cleavage products. Such a molecule explained the older conceptions of protein metabolism. The work of Hofmeister, Kossel, and Emil Fischer first gave a true insight into the composition of the protein molecule. One must know the life history of sixteen amino-acids in order to be familiar with the metabolism of protein. Though the extension of knowledge may have been at the cost of simplicity, yet order is being wrought out of apparent complexity. It is often difficult for an older generation to think in terms of the knowledge of a new. The author's father was a student at Heidelberg at the time when the modern chemical formulæ were introduced, when H—O became H_2O, and he recalled the distracted exclamation of one of the university professors, "Ach Gott! wie kann man so lernen!"

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[1] Pflüger and Junkersdorf: "Pflüger's Archiv," 1910, cxxxi, 201.

The intimate knowledge of the behavior of the amino-acids within the body may be studied by a variety of means.

1. The direct removal in the urine of certain of the amino-acids, such as glycocoll and cystein, or the removal of slightly changed products, such as homogentisic acid from tyrosin and kynurenic acid from tryptophan.

2. The determination in the urine of a dog made diabetic by phlorhizin of the quantity of "extra glucose" eliminated after the ingestion of certain amino-acids, and the determination of an increase in the quantity of β-oxybutyric acid after the administration of other amino-acids under like conditions.

3. The results of experiments in which an amino-acid is added to warmed oxygenated blood and this perfused through a surviving liver, subsequent analysis of the blood revealing any chemical change which the material might have undergone.

It should be remembered that when amino-acids are ingested the resulting nitrogen increase in the urine is entirely due to urea.[1] The same is true of the dipeptid glycyl-glycin[2] (see p. 75). It is believed that the deamination of an amino-acid results in the formation of ammonia, which, becoming ammonium carbonate, may be converted into urea. Yet experiments *in vitro* have failed to demonstrate this action. Gertrude Bostock[3] found that the liver and intestinal mucosa failed to deaminize alanin. Levene and Meyer[4] find that leukocytes and kidney tissue do not deaminize glycocoll, alanin, aspartic acid, and leucin. Griesbach and Oppenheimer[5] are of the same opinion. Thus the *characteristic biologic reaction of deamination is effected through the activity of living tissue cells.* Special enzymes are nowhere in evidence.

For the understanding of the biochemic relations of the

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[1] Levene and Kober: "American Journal of Physiology," 1909, xxiii, 324.

[2] Levene and Meyer: *Ibid.*, 1909–10, xxv, 214.

[3] Bostock: "Biochemical Journal," 1911, vi, 48.

[4] Levene and Meyer: "Journal of Biological Chemistry," 1913, xv, 65; 1913–14, xvi, 555.

[5] Griesbach and Oppenheimer: "Biochemische Zeitschrift," 1913, lv, 329.

various amino-acids it seems desirable to present as briefly as possible the laws governing their fate in the organism.[1]

THE PROCESS OF DEAMINATION

The nature of the attack of the living cell upon the NH_2 group of the amino-acids has been the subject of much investigation. The process was at first thought to be one of simple hydrolysis, as follows:

$$R-CHNH_2-COOH + HOH = R-CHOH-COOH + NH_3$$

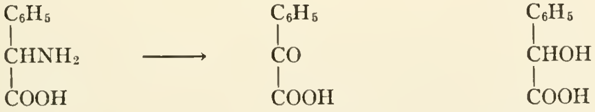
After this fashion glycocoll, $CH_2NH_2—COOH$, would become glycollic acid, $CH_2OH—COOH$; alanin, $CH_3—CHNH_2—COOH$, would become lactic acid, $CH_3—CHOH—COOH$, and so forth.

It was Otto Neubauer,[2] in the laboratories of the second medical clinic of the University of Munich, who first showed that the process of *deamination* might be one of *oxidation* and not hydrolysis. This process of *oxidative deamination* is represented in the following formula:

$$R-CHNH_2-COOH + O = R-CO-COOH + NH_3$$

From glycocoll, $CH_2NH_2—COOH$, one would thus obtain glyoxylic acid, $CHO—COOH$; and from alanin, $CH_3—CHNH_2—COOH$, pyruvic acid, $CH_3—CO—COOH$.

That this method of oxidation is actually possible in the organism was evident when Neubauer gave phenyl-glycocoll to a dog and found phenyl-glyoxylic acid as well as mandelic acid in the urine.



$$\begin{array}{c} C_6H_5 \\ | \\ CHNH_2 \\ | \\ COOH \end{array} \longrightarrow \begin{array}{c} C_6H_5 \\ | \\ CO \\ | \\ COOH \end{array} \qquad \begin{array}{c} C_6H_5 \\ | \\ CHOH \\ | \\ COOH \end{array}$$

Phenyl-glycocoll. Phenyl-glyoxylic acid. Mandelic acid.

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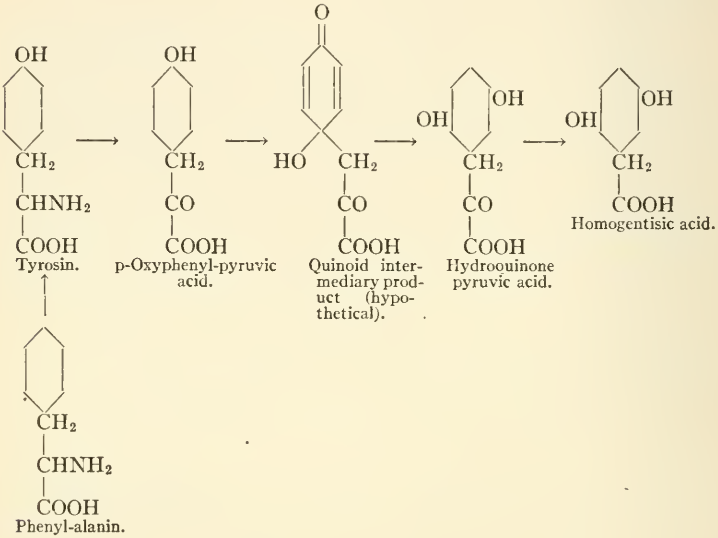
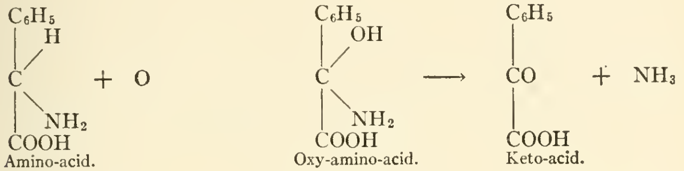
[1] For excellent reviews, see Dakin: "Oxidations and Reductions in the Animal Body," Longmans, Green and Co., 1912; Underhill, "The Physiology of the Amino-Acids," Yale University Press, 1915.

[2] Neubauer: "Deutsches Archiv für klinische Medizin," 1909, xcv, 211.

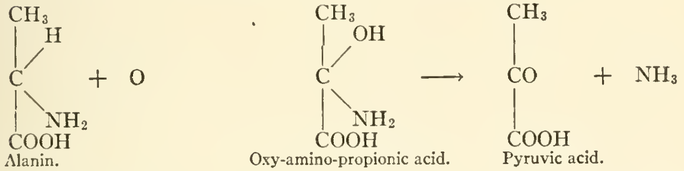
Further evidence was obtained by Neubauer through the medium of a rare anomaly of human metabolism called *alcaptonuria* (see p. 196). In this disease tyrosin and phenyl-alanin are not oxidized to their usual end-products, but are eliminated in the urine as *homogentisic acid.* The transformation of phenyl-alanin and tyrosin into homogentisic acid is believed to follow the scheme presented below:



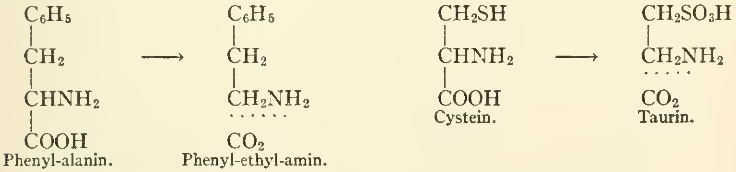
It will be noted that the alanin radicle, $CH_2—CHNH_2—COOH$, is represented as undergoing oxidative deamination, being converted into pyruvic acid. Neubauer drew this conclusion from the fact that if phenyl-alanin, tyrosin, or p-oxy-phenyl-pyruvic acid were given to the alkaptonuric patient they all appeared in the urine as homogentisic acid, whereas when p-oxy-phenyl-lactic acid was given there was no increase in the homogentisic acid excretion whatever. Consequently it could not have been an intermediary product in the metabolism of tyrosin. Neubauer, therefore, concluded that the primary pathway of deamination was oxidative and not hydrolytic. Later he[1] presented the following formula as indicating the probable reaction of oxidative deamination:



Alanin, for example, would follow this pathway:



Examination of the formula given for the conversion of phenyl-alanin into homogentisic acid shows that the alanin radicle of phenyl-alanin is converted into an acetic acid radicle in homogentisic acid. The question arises whether the first step in the destruction of phenyl-alanin might not be the loss of its acid group by CO_2 cleavage, as indeed happens when it is acted upon by bacteria,[2] and as is usual in the transformation of cystein into taurin.



As phenyl-ethyl-amin is poisonous, its first oxidation product, phenyl-ethyl-alcohol, was given by Neubauer to the alkaptonuric, but without increasing the quantity of homogentisic acid. It appeared in the urine as phenyl-acetic acid

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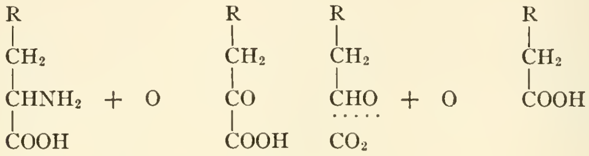
[1] Neubauer and Fromherz: "Zeitschrift für physiologische Chemie," 1910, lxx, 326.

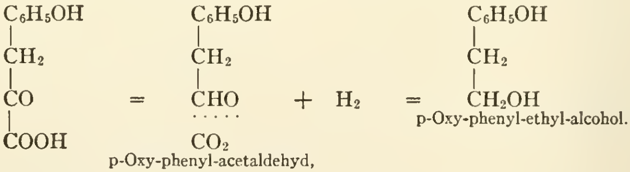
[2] Spiro: "Hofmeister's Beiträge," 1902, i, 347.

(paired with glycocoll). This indicates that oxidative deamination takes place in the metabolism of phenyl-alanin before CO_2 is split from the acid radicle. The CO_2 cleavage follows deamination, as appears in the formula given for the transformation of hydroquinone-pyruvic acid into homogentisic acid. It follows from this that after the oxidative deamination of an amino-acid, the deaminized remainder may be converted into an acid containing one less carbon atom, as follows:



$$\begin{array}{l}\mathrm{R}\\|\\\mathrm{CH_2}\\|\\\mathrm{CHNH_2}\\|\\\mathrm{COOH}\end{array} + \mathrm{O} \qquad \begin{array}{l}\mathrm{R}\\|\\\mathrm{CH_2}\\|\\\mathrm{CO}\\|\\\mathrm{COOH}\end{array} \quad \begin{array}{l}\mathrm{R}\\|\\\mathrm{CH_2}\\|\\\mathrm{CHO}\\\cdots\cdots\\\mathrm{CO_2}\end{array} + \mathrm{O} \qquad \begin{array}{l}\mathrm{R}\\|\\\mathrm{CH_2}\\|\\\mathrm{COOH}\end{array}$$

If after producing the aldehyde by CO_2 cleavage, *reduction* prevails instead of oxidation, then an alcohol is formed instead of an acid. This may be illustrated by the work of F. Ehrlich,[1] who found that when yeast acted on tyrosin the end-product was p-oxy-phenyl-ethyl-alcohol, $OH—C_6H_4—CH_2$-CH_2OH. Neubauer and Fromherz, continuing their theoretic researches, discovered that yeast acting on p-oxy-phenyl-pyruvic acid yields this same ethyl-alcohol derivative, while p-oxy-phenyl-lactic acid does not give it. Para-oxy-phenyl-pyruvic acid may, therefore, be transformed as follows:



$$\begin{array}{l}\mathrm{C_6H_5OH}\\|\\\mathrm{CH_2}\\|\\\mathrm{CO}\\|\\\mathrm{COOH}\end{array} = \begin{array}{l}\mathrm{C_6H_5OH}\\|\\\mathrm{CH_2}\\|\\\mathrm{CHO}\\\cdots\cdots\\\mathrm{CO_2}\end{array} + \mathrm{H_2} = \begin{array}{l}\mathrm{C_6H_5OH}\\|\\\mathrm{CH_2}\\|\\\mathrm{CH_2OH}\end{array}$$

p-Oxy-phenyl-acetaldehyd, p-Oxy-phenyl-ethyl-alcohol.

Although p-oxy-phenyl-lactic acid is not acted on by yeast, yet it also appears as a product when yeast acts on p-oxy-phenyl-pyruvic acid. Hence pyruvic acid may be reduced, with the formation of lactic acid.

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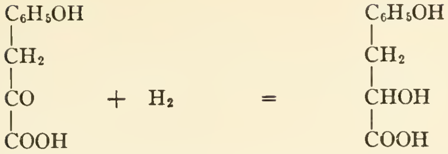
[1] Ehrlich, F.: "Ber. d. d. chem. Ges.," 1907, xl, 1047.

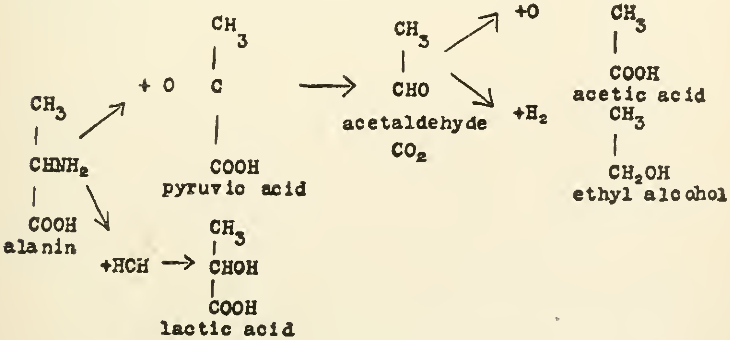


$$\begin{array}{c} C_6H_5OH \\ | \\ CH_2 \\ | \\ CO \\ | \\ COOH \end{array} + H_2 = \begin{array}{c} C_6H_5OH \\ | \\ CH_2 \\ | \\ CHOH \\ | \\ COOH \end{array}$$

In conformity with this stands the observation of P. Mayer,[1] who found that if pyruvic acid were administered to a rabbit lactic acid appeared in the urine.

Although it appears certain that oxidative deamination is the principal method of attack upon the amino group of the aromatic acids, yet direct hydrolytic deamination has been noted for them, and it may play a considerable rôle in the metabolism of the amino-acids of the aliphatic series as well. Neubauer finds the lævo-component of p-oxy-phenyl-lactic acid in the urine of a patient suffering from cirrhosis of the liver. Since the dextro-component is always eliminated in the human being whenever it is formed by reduction of p-oxy-phenyl-pyruvic acid within the organism, it follows that this latter substance could not have been the intermediary one, but that the l-compound was formed by the direct hydrolytic cleavage of l-tyrosin.

These reactions give one an insight into oxidations, reductions, hydrolyses, and cleavages, which are of constant occurrence as the result of vital activities. One may summarize all these possible biologic variations in the following scheme, using alanin as a typical amino-acid:



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[1] Mayer, P.: "Biochemische Zeitschrift," 1912, xl, 441.

It has been noted by Kotake[1] that although p-oxy-phenyl-pyruvic acid is completely oxidized when administered to a rabbit, p-oxy-phenyl-lactic acid remains almost untouched and appears in the urine. The fact, however, that lactic acid and alanin pass over into sugar much more readily than does pyruvic acid leads Ringer[2] to believe that the metabolism of alanin probably follows the path of hydrolytic deamination into lactic acid rather than that of oxidative deamination into pyruvic acid.

The reader should realize that there are many possible pathways in metabolism, and the above presentation may be regarded as suggestive rather than literally exact.

THE OXIDATION OF FATS

In order to be able to understand the further fate of some of the deaminized remainders of the amino-acids, the method of oxidation of fatty acids must be understood. The experiments of Knoop[3] are based on the fact that benzoic acid, C_6H_5COOH, when given to an animal pairs with glycocoll and appears as hippuric acid in the urine, whereas phenylacetic acid, $C_6H_5CH_2COOH$, when given pairs in the same way and is eliminated as phenaceturic acid. Knoop found that whenever aromatic derivatives of the fatty acids were given to an animal one of these two forms always appeared in the urine; that if the side chain had an odd number of carbon atoms hippuric acid was always the end-result, and if there were an even number of atoms phenaceturic acid appeared as the final product.

The following substances were given:

$$C_6H_5\text{—}CH_2\text{—}CH_2\text{—}\underset{\beta}{CH_2}\text{—}CH_2\text{—}COOH \quad \text{Phenylvalerianic acid.}$$

$$C_6H_5\text{—}CH_2\text{—}\underset{\beta}{CH_2}\text{—}CH_2\text{—}COOH \quad \text{Phenylbutyric acid.}$$

$$C_6H_5\text{—}\underset{\beta}{CH_2}\text{—}CH_2\text{—}COOH \quad \text{Phenylpropionic acid.}$$

[1] Kotake: "Zeitschrift für physiologische Chemie," 1910, lxix, 409.
[2] Ringer: "Journal of Biological Chemistry," 1913, xv, 145.
[3] Knoop: "Hofmeister's Beiträge," 1905, vi, 150.

Since phenylvalerianic and phenylpropionic acids both yielded hippuric acid and phenylbutyric did not, it was evident that the last named was not an intermediary product between the first two. Knoop, therefore, concluded that in the oxidation of fats the β-carbon atom was oxidized and that two carbon atoms dropped from the chain together. This view was supported by Dakin's[1] discovery that when phenylpropionic acid was given in large amounts phenyl-β-oxy-propionic acid, $C_6H_5—CHOH—CH_2—COOH$, was detected in the urine. Corroborative evidence is further found in the fact that when body fat or food fat, both of which always contain an even number of carbon atoms, are metabolized in the diabetic, the end-product is always β-oxybutyric acid, $CH_3CHOHCH_2COOH$, which one would expect in terms of the theory.

It is interesting to note the results of giving the following three substances:

$$C_6H_5COCH_2COOH \longrightarrow C_6H_5COOH$$
$$C_6H_5CH_2COCOOH \longrightarrow \text{oxidized}$$
$$C_6H_5COCH_2CH_2COOH \longrightarrow C_6H_5CH_2COOH$$

Phenyl-β-keto-propionic acid is oxidized on the β-carbon atom to benzoic acid. Phenyl-α-keto-propionic acid (phenylpyruvic acid), as stated, is completely oxidized in the organism, while phenyl-γ-keto-butyric acid undergoes reduction of its γ-carbon and oxidation of its β-carbon and is eliminated in the urine as phenyl-acetic acid. Here reduction and oxidation play alternately upon the same molecule.

The oxidation of *unsaturated fatty acids*, or such as have a double linkage between two carbon atoms, follows the same laws as the oxidation of saturated fatty acids. Thus, Erdmann and Marchand[2] found that if cinnamic acid, $C_6H_5.CH:CH.COOH$, be given to an animal, benzoic acid appears in the urine. Dakin[3] administered the material in large doses to cats and found the intermediary oxidation product, phenyl-β-oxy-propionic acid, $C_6H_5.CHOH.CH_2COOH$, in the urine.

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[1] Dakin: "Journal of Biological Chemistry," 1909, vi, 203.

[2] Erdmann and Marchand: "Liebig's Annalen," 1842, xliv, 344.

[3] Dakin: "Oxidations and Reductions in the Animal Body," 1912, p. 36.

This preliminary discussion has shown that amino-acids are oxidized at the α-position which is the point of attachment of the NH_2 group, and are converted into oxy- or keto-acids and then into acids having one less carbon atom. After this the organic acid becomes subject to the laws of β-oxidation, under which a fatty acid is oxidized on its β-carbon atom, oxy- and keto-acids being first formed, and then there is cleavage of two carbon atoms with the formation of an acid which contains two less carbon radicles than before. Frequently β-oxybutyric acid is an intermediary product of this oxidation, just as happens in the case of fatty acids. In other cases in which the product contains three atoms of carbon, the end-product may be converted into glucose in the organism. Ringer[1] has demonstrated that in the β-oxidation of fatty acids having uneven numbers of carbon atoms sugar is formed from them in the diabetic organism in proportion to the power to produce propionic acid, $CH_3.CH_2.COOH$. This might form β-lactic acid, $CH_2OH.CH_2COOH$, which, in turn, might be converted into glucose.

Experiments have shown that the glucose-forming amino-acids include glycocoll, alanin, prolin, aspartic and glutamic acids, serin, cystin, and arginin. Some of the other amino-acids yield β-oxybutyric acid as an intermediary product.

It seems desirable at this point to enter into the more intimate details of the life-history of the different amino-acids. Though the general energy metabolism may be understood without this knowledge, yet the finer comprehension of the subject cannot be otherwise obtained.

THE FATE OF THE AMINO-ACIDS

Glycocoll ($CH_2NH_2.COOH$).—*Probably both carbon atoms are able to enter into the formation of glucose. Present in most proteins; in large amount in gelatin; absent in milk proteins and in gliadin of wheat.*

It has been noted that when benzoic acid is administered to

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[1] Ringer: "Journal of Biological Chemistry," 1913, xiv, 43.

an animal it forms a synthetic compound with glycocoll within the organism which is eliminated in the urine as hippuric acid.

$$C_6H_5.COOH + CH_2.NH_2.COOH = C_6H_5CO.NHCH_2.COOH + H_2O.$$

Hippuric acid is found in the urine of horses and cattle in the food of which materials convertible into benzoates are found. It is eliminated almost as soon as it is formed, for Lewis[1] found after administering hippuric acid to a man that 82 per cent. could be recovered in the urine within three hours.

Lewinski[2] found that when 10 or 20 grams of benzoic acid were administered to a man in the form of sodium benzoate the entire quantity of benzoic acid was combined and eliminated in the form of hippuric acid. Only when the power to form glycocoll was exceeded was there an elimination of benzoic acid. Thus, after giving 50 grams of benzoic acid, 62.3 grams of hippuric acid containing 42.3 grams of combined benzoic acid were eliminated, together with 8.2 grams of uncombined acid.

The following data are taken from Lewinski's experiments upon the same individual when partaking of low and of high protein diets. The figures are for twenty-four hours:

Benzoic Acid Administered. Grams.	Total N in Urine. Grams.	Hippuric Acid N. Grams.	$\frac{HN}{TN}$
25	9.3	2.74	29.4
40	9.0	3.15	34.9
40	23.7	4.06	18.0
50	29.1	4.87	18.6

When there were 9 grams of total nitrogen eliminated, 3.15 grams or 35 per cent. appeared in the form of glycocoll. When 29 grams of total nitrogen, only 4.87 grams of nitrogen appeared in the form of glycocoll. In other words, an increase of 20 grams of nitrogen in the urine was accompanied by an increase of 1.72 grams of glycocoll nitrogen, which is only 8.5 per cent. of the increase in protein metabolism instead of 35 per cent.

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[1] Lewis: "Journal of Biological Chemistry," 1914, xviii, 225.

[2] Lewinski: "Archiv für ex. Path. und Pharm.," 1908, lviii, 397. See also Dakin: "Journal of Biological Chemistry," 1909–10, vii, 103.

Magnus-Levy[1] found that 25 to 27 per cent. of the total urinary nitrogen of rabbits fed with cream and of a goat fed with hay is excreted in the form of hippuric acid when benzoate of soda is administered with the food. He calculated that only 4 per cent. of this could have been derived from glycocoll preformed in the protein metabolized, but that 20 per cent. could have originated from leucin did this pass through a glycocoll stage.

It has already been stated that the individual amino-acids lose their nitrogen as the first step in their metabolism. Only by the union of its nitrogen atom with benzoic acid is glycocoll spared this fate. One might believe that other amino-acids might unite with benzoic acid in a similar fashion, and then be converted into hippuric acid by oxidation of the rest of their carbon chains. To test this hypothesis, Magnus-Levy[2] administered subcutaneously benzoylated compounds of alanin, valin, leucin, phenylalanin, aspartic acid, glutamic acid, ornithin, and serin. He found that these compounds were not changed into hippuric acid in the organism, but were eliminated unchanged in the urine.

These experiments were a further demonstration that in the breaking down of amino-acids deamination is the first step, and they leave no conclusion open other than that *glycocoll arises by a synthetic process.*

The nature of the process is still a riddle. The great elimination of glycocoll in hippuric acid has been repeatedly observed by Wiechowski[3] and by Ringer,[4] the latter finding that 38 per cent. of the total nitrogen may be eliminated as hippuric-acid nitrogen in the fasting goat. Parker and Lusk[5] suggested the synthetic origin of glycocoll, but reported that carbohydrates had no influence on the excretion of hippuric acid. Abderhalden and Strauss[6] gave a pig which was nourished

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[1] Magnus-Levy: "Münchener medizinische Wochenschrift," 1905, lii, 2168.

[2] Magnus-Levy: "Biochemische Zeitschrift," 1907, vi, 541.

[3] Wiechowski: "Hofmeister's Beiträge," 1906, vii, 204.

[4] Ringer: "Journal of Biological Chemistry," 1911, x, 327.

[5] Parker and Lusk: "Amer. Jour. of Physiology," 1899–1900, iii, 472.

[6] Abderhalden and Strauss: "Zeitschrift für physiologische Chemie," 1914, xci, 81.

on bran and potatoes 12 grams of sodium benzoate daily, and during certain periods added glycocoll, alanin, and ammonium carbonate. The results were as follows:

Period.	No. of Days.	Added to Food.	Hippuric Acid in Urine 24 Hours.
V	8	....	2.54
VI	8	Glycocoll, 12 g.	4.51
VII	6	....	3.30
VIII	12	Alanin, 12 g.	3.30
IX	6	....	2.63
X	18	Ammonium carbonate, 15.6 g.	2.20

From this it appears that glycocoll when given with the benzoate is far from being completely removed in the urine, and that neither alanin which yields ammonia on deamination nor ammonium carbonate itself have any effect whatever on the elimination of glycocoll.

McCollum and Hoagland[1] have reported some remarkable experiments. A pig, weighing 46.7 kilograms, was brought into a condition of minimal nitrogen metabolism by giving a diet of starch containing 75 calories for each kilogram of body weight. The diet was then continued and increasing amounts of benzoic acid were added. Finally, hydrochloric acid and benzoic acid were given together. The results of the urinary analyses are here reproduced:

Period.	No. of Days.	Food.	Total N.	Urea N.	NH_3-N.	Creatinin N.	Other N.*
I	12	Starch, 75 cal. per kg. alk. salts.	2.56	1.43	0.21	0.488	0.424
II	4	Same + 4 g. benzoic acid.	2.63	1.29	0.21	0.456	0.681
III	7	Same + 10 g. benzoic acid.	2.23	0.58	0.22	0.484	0.948
IV	5	Same + 16 g. benzoic acid.	2.86	0.55	0.38	0.437	1.492
V	5	Starch same, neut. salts + 16 g. benzoic acid + 10 g. 25 per cent. HCl.	4.03	0.54	1.44	0.424	1.632

* This includes hippuric acid.

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[1] McCollum and Hoagland: "Journal of Biological Chemistry," 1913–14, xvi, 299. See also Lewis: *Ibid.*, 1914, xviii, 225.

It is evident from this that when the protein metabolism is reduced to a minimal level by carbohydrate ingestion (see p. 273) the addition of benzoic acid does not affect the creatinin output, scarcely affects the total nitrogen elimination, but may reduce the total elimination of urea nitrogen from 56 per cent. of the total nitrogen output to 19 per cent. of the total. This difference, or 37 per cent., of the total nitrogen which is ordinarily converted into urea is under these circumstances eliminated as glycocoll. It is of great significance that this is accomplished without materially changing the amount of protein metabolism (see p. 286). Giving hydrochloric acid with benzoic acid greatly increases ammonia formation, but scarcely influences the other urinary constituents (see p. 219). The urea elimination remains at its former minimal level.

This discussion has shown that one may compute that 35, 37, and 38 per cent. of the total endogenous protein metabolism of man, goat, and pig may pass through a glycocoll stage and be eliminated in the urine. It is certain that no protein contains this quantity of glycocoll. In spite of all the work accomplished there is no solution of the problem from what materials this synthetic production of glycocoll occurs. It arises as does creatinin without having as yet betrayed the secret of its origin. The synthetic production of glycocoll is of undoubted value in making possible the development of body tissue which contains glycocoll from milk proteins which are free from it.

Glycocoll forms sugar in the organism. Ringer and Lusk[1] found that it was completely converted into glucose in the phlorhizinized dog.

The method employed is to give to a dog, rendered diabetic by phlorhizin and then almost glycogen free by shivering, the material to be tested, and to observe the increased output of glucose in the urine. One may give glucose itself and witness its complete elimination,[2] as follows:

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[1] Ringer and Lusk: "Zeitschrift für physiologische Chemie," 1910, lxvi, 106.

[2] Taken from Csonka: "Journal of Biological Chemistry," 1915, xx, 543.

Period.	Glucose.	Nitrogen.	D : N.	Extra Glucose.
Preliminary	.....	....	3.68	
Glucose, 16 g.	25.92	2.87	9.00	15.43
After period	.....	....	3.54	

There were 2.87 grams of nitrogen in the urine of seven hours. Assuming the customary D:N = 3.65 : 1 (see p. 174), then the quantity of glucose derived from the metabolism of protein during the seven hours would be 2.87 × 3.65 = 10.49 grams. Deducting 10.49 grams from 25.92 grams found in the urine, it appears that 15.43 grams of extra sugar were eliminated during the period of experimentation.

In the case of glycocoll the results may be thus analyzed:

Period	Glucose.	Nitrogen.	D : N.	Extra Glucose.
Preliminary	.....	.....	3.40	
Glycocoll, 20 g.	47.42	14.84	3.20	16.63
After period	.....	.....	3.37	

During a period of fourteen hours following the ingestion of 20 grams of glycocoll containing 3.73 grams of nitrogen 14.84 grams of nitrogen appeared in the urine. The difference or 9.11 grams represents the nitrogen of the protein metabolism. Multiplying this by the prevailing D : N = 3.38, one obtains 9.11 × 3.38 = 30.79 grams of glucose which could have arisen from the protein metabolism of the time. Since 47.42 grams were actually eliminated, it follows that the difference or 16.63 grams of glucose derived their origin from glycocoll.

The reaction showing this conversion of glycocoll into glucose may thus be written, carbon dioxid being neutralized by ammonia liberated from glycocoll and the compound converted into urea.

$$\begin{array}{ll} 6C_2H_5NO_2 + 3CO_2 + 3H_2O & = 2C_6H_{12}O_6 + 3CH_4N_2O + 3O_2 \\ \text{20 g. glycocoll} & = \text{16 g. glucose} + \text{8 g. urea} \end{array}$$

It should be noted that Cremer[1] believes that only three-quarters of the carbon passes over into glucose and holds the following reaction to be the more probable:

$$\begin{array}{lcl} 4C_2H_5NO_2 & = & C_6H_{12}O_6 + 2CH_4N_2O \\ \text{20 g. glycocoll} & = & \text{12 g. glucose} + \text{8 g. urea} \end{array}$$

By what method may this reaction be accomplished? It has been shown that deamination results in the formation of either glyoxylic acid, $CHO.COOH$, or glycollic acid, $CH_2OH.COOH$. These materials must be reduced if they are to form glucose.

Haas[2] could find no evidence of reduction of glyoxylic to either glycollic or acetic acid in the organism, nor was glycocoll formed synthetically from it by union with ammonia. Nor could Honjio[3] find any indication of acetic acid formation after perfusing a liver with glycollic acid. Also, the synthesis of glycollic acid into glycocoll in the organism cannot be accomplished.[4]

If glycollic acid be the product of deamination, as appears most probable, its first reduction product would be glycol aldehyd.

$$CH_2OH.COOH + H_2 = CH_2OH.CHO + H_2O$$

Glycol aldehyd in aqueous solution is polymerized with the formation of sugar,[5] $C_6H_{12}O_6$. If administered by subcutaneous injection to a rabbit it leads to an output of sugar in the urine.[6] When perfused through the liver of a tortoise[7] or of a dog[8] glycol aldehyd is converted into glycogen. If glycol aldehyd be slowly administered to phlorhizinized dogs, as much as 75 per cent. may escape oxidation and be converted into glucose.[9]

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[1] Cremer: "Medizinische Klinik," 1912, viii, 2050.

[2] Haas: "Biochemische Zeitschrift," 1912, xlvi, 298.

[3] Honjio: *Ibid.*, 1914, lxi, 286.

[4] Sassa: *Ibid.*, 1913–14, lix, 353.

[5] Neuberg and Rewald: "Biochemische Handlexikon," ii, 266.

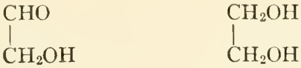
[6] Mayer: "Zeitschrift für physiologische Chemie," 1903, xxxviii, 151.

[7] Parnas and Baer: "Biochemische Zeitschrift," 1912, xli, 392.

[8] Barrenscheen: *Ibid.*, 1913, lviii, 300.

[9] Sansum and Woodyatt: "Journal of Biological Chemistry," 1914, xvii, 521.

It is suggestive in this connection to remember that Neuberg[1] has shown that yeast zymases may reduce this simplest of all the oxy-aldehyds into ethylen glycol:



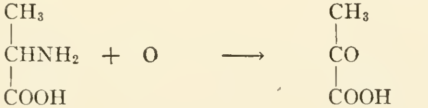
$$\begin{array}{l} CHO \\ | \\ CH_2OH \end{array} \qquad \begin{array}{l} CH_2OH \\ | \\ CH_2OH \end{array}$$

d-Alanin ($CH_3.CHNH_2.COOH.$)—*All three carbon atoms are able to enter into the formation of glucose. Found in all true proteins. In zein as much as 13.4 per cent., in muscle protein about 8 per cent. is present.*

Neuberg[2] found glycogen in the liver and lactic acid in the urine of a normal rabbit following the ingestion of alanin. The amino-acid had been converted into lactic acid with the elimination of ammonia. Ringer and Lusk[3] gave 20 grams of i-alanin to a phlorhizinized dog and witnessed its complete elimination in the form of urinary glucose. Dakin[4] obtained the same result after administering l-alanin.

Mandel and Lusk[5] showed that d-lactic acid was completely converted into glucose in the diabetic organism and as much as 70 per cent. of the d-l-lactic acid could be transformed.

Dakin has emphasized the fact that these experiments demonstrate that the loss of asymmetry of the central carbon atom of l-alanin or of l-lactic acid is essential for the formation of d-glucose. Such a loss of asymmetry would occur in the case of alanin if it were converted into pyruvic acid by oxidative deamination.



$$\begin{array}{l} CH_3 \\ | \\ CHNH_2 \\ | \\ COOH \end{array} + O \longrightarrow \begin{array}{l} CH_3 \\ | \\ CO \\ | \\ COOH \end{array}$$

Alanin. Pyruvic acid.

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[1] Neuberg: "Biochemische Zeitschrift," 1915, lxxi, 1.

[2] Neuberg and Langstein: "Archiv für Physiologie," 1903, Suppl. Bd., p. 514.

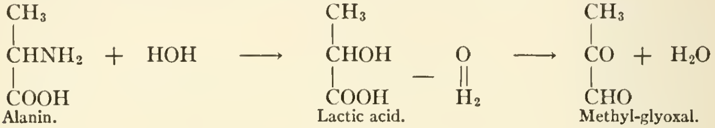
[3] Ringer and Lusk: *Loc. cit.*

[4] Dakin and Dudley: "Journal of Biological Chemistry," 1914, xvii, 451.

[5] Mandel and Lusk: "American Journal of Physiology," 1906, xvi, 129.

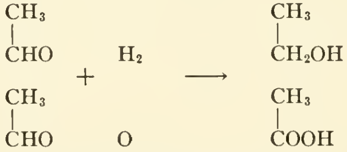
This is a possible pathway, for pyruvic acid is convertible into glucose when administered to the glycosuric organism.[1] Levene[2] finds that aseptic preparations of leukocytes or kidney tissue effect no chemical change of pyruvic acid, this being contrary to the action of yeast cells which converts it into acetaldehyd with cleavage of CO_2 (see p. 267).

If alanin be convertible into lactic acid by hydrolysis, the asymmetry of the central carbon atom could be eliminated by a *reversed internal Cannizzaro reaction*, as follows:



$$\underset{\text{Alanin.}}{\begin{array}{l}CH_3\\ |\\ CHNH_2\\ |\\ COOH\end{array}} + HOH \longrightarrow \underset{\text{Lactic acid.}}{\begin{array}{l}CH_3\\ |\\ CHOH\\ |\\ COOH\end{array}} - \begin{array}{c}O\\ \|\\ H_2\end{array} \longrightarrow \underset{\text{Methyl-glyoxal.}}{\begin{array}{l}CH_3\\ |\\ CO\\ |\\ CHO\end{array}} + H_2O$$

The *Cannizzaro reaction* involves the conversion of two molecules of aldehyd into one of acid and one of alcohol through the mediation of water. Thus, Batelli and Stern[3] observed that tissue converted acetaldehyd into alcohol and acetic acid.



$$\begin{array}{l}CH_3\\ |\\ CHO\\ CH_3\\ |\\ CHO\end{array} + \begin{array}{c}H_2\\ \\ O\end{array} \longrightarrow \begin{array}{l}CH_3\\ |\\ CH_2OH\\ CH_3\\ |\\ COOH\end{array}$$

The enzyme accomplishing this reaction is called "aldehyd mutase" by Parnas.[4]

The *internal Cannizzaro reaction* deals with the oxidation of aldehyd and reduction of the keto radicles in the same compound. This may be illustrated by the conversion of methyl glyoxal into lactic acid, which Dakin[5] and Neuberg[6] have shown is rapidly effected by tissue in vitro. Dakin calls

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[1] Ringer: "Journal of Biological Chemistry," 1913, xv, 145; 1914, xvii, 281; Dakin and Janney: *Ibid.*, 1913, xv, 177; Cremer: "Berliner klinische Wochenschrift," 1913, l, 1457.

[2] Levene and Meyer: "Journal of Biological Chemistry," 1914, xvii, 443.

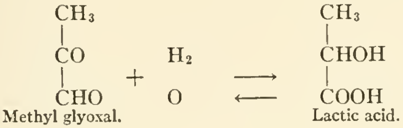
[3] Batelli and Stern: "Compt. rend. soc. biol.," 1910, lxviii, 742.

[4] Parnas: "Biochemische Zeitschrift," 1910, xxviii, 274.

[5] Dakin and Dudley: "Journal of Biological Chemistry," 1913, xiv, 155, 423.

[6] Neuberg: "Biochemische Zeitschrift," 1913, xlix, 502.

the enzymes accomplishing these reactions "glyoxylases," while Neuberg prefers the name "keto-aldehyd mutase."

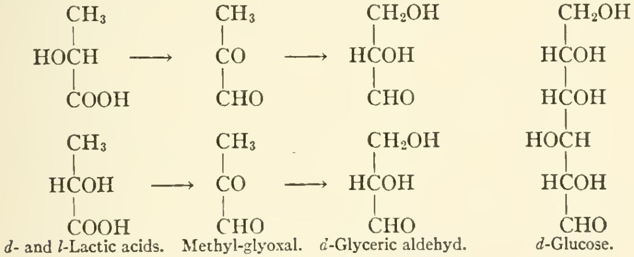


$$CH_3{-}CO{-}CHO + H_2O \rightleftarrows CH_3{-}CHOH{-}COOH$$

The reversed internal Cannizzaro reaction accomplishes the conversion of lactic acid into methyl-glyoxal.

Dakin[1] gave 9 grams of methyl glyoxal to a phlorhizinized dog and obtained 7 grams of extra sugar in the urine, while 12 grams of l-lactic acid yielded 9 grams of extra glucose.

These experiments enabled Dakin to picture the transformation of a d-l-alanin through d-l-lactic acid into d-glucose, as follows:



$$CH_3{-}HOCH{-}COOH \longrightarrow CH_3{-}CO{-}CHO \longrightarrow CH_2OH{-}HCOH{-}CHO$$

$$CH_3{-}HCOH{-}COOH \longrightarrow CH_3{-}CO{-}CHO \longrightarrow CH_2OH{-}HCOH{-}CHO$$

$$CH_2OH{-}HCOH{-}HCOH{-}HOCH{-}HCOH{-}CHO$$

Neuberg[2] reached essentially similar conclusions.

Ringer and Lusk[3] showed that glyceric acid was convertible into glucose in the phlorhizinized dog, and the same was shown for glyceric aldehyd by Woodyatt.[4]

It has been difficult to find a chemical analogy to the transformation of the CH_3 group of methyl-glyoxal into $-CH_2OH$ in glycerin aldehyd. It is certain that the CH_3 groups in lactic acid and alcohol both arise in biochemical reactions from glucose, yet the manner of origin is unknown.[5]

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[1] Dakin and Dudley: "Journal of Biological Chemistry," 1913, xv, 127.

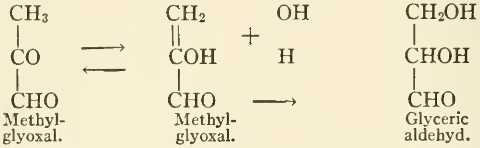
[2] Neuberg: "Biochemische Zeitschrift," 1913, li, 484.

[3] Ringer and Lusk: "*Loc. cit.*

[4] Woodyatt: "Journal of Biological Chemistry," 1915, xxi, 1.

[5] Neuberg and Rewald: "Biochemische Zeitschrift," 1914, lxvii, 127.

Dakin (oral statement to the writer) presents a solution of the problem dependent upon the interconversion of tautomeric forms of methyl-glyoxal:



Since fructose[1] and many other hexose sugars yield methyl-glyoxal with readiness *in vitro*, there is much likelihood that this is the intermediary substance produced when fructose and galactose, for example, are converted into glucose by the diabetic or into glycogen (which yields glucose) in the normal organism. The above described transformation, first postulated by Nef,[2] is, therefore, of fundamental biologic significance not only in the metabolism of alanin but also as regards that of carbohydrate.

It may be added that alanin may be formed synthetically from pyruvic acid,[3] when this substance is perfused through the liver, or from glycogen[4] when an ammonium salt is perfused through a liver rich in glycogen.

It appears from this analysis that the amino-acid alanin yields on deamination an acid which may readily be converted into glucose or into methyl-glyoxal, a direct cleavage product of glucose, and which, therefore, may behave like glucose in the organism. Consideration of the oxidation of glucose will be found in Chapter IX.

Valin ($(CH_3)_2$: $CH.CHNH_2.COOH$).—*Present in small amounts in most proteins. Fate obscure.*

By the method of liver perfusion, Embden, Salomon, and Schmidt[5] could find no acetone bodies arising from valin.

[1] Wohl: "Biochemische Zeitschrift," 1907, v, 45.

[2] Nef: "Liebig's Annalen," 1904, cccxxxv, 247.

[3] Embden and Schmitz: "Biochemische Zeitschrift," 1911–12, xxxviii, 393.

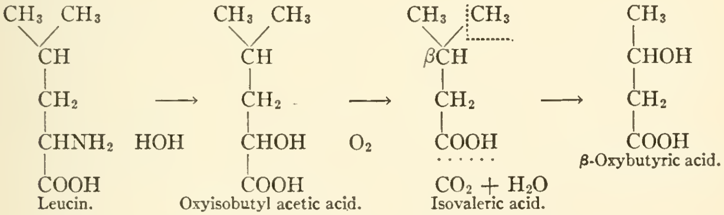
[4] Fellner: *Ibid.*, 1911–12, xxxviii, 414.

[5] Embden, Salomon, and Schmidt: "Hofmeister's Beiträge," 1906, viii, 129.

Dakin[1] gave valin to a phlorhizinized dog, but could find no clear evidence of glucose or β-oxybutyric acid formation from it. Its oxy-acid, α-oxy-isovalerianic acid, also yielded little or no sugar.

Leucin ($(CH_3)_2$: $CH.CH_2.CHNH_2COOH$).—*Present in all proteins. Convertible into β-oxybutyric acid.*

Leucin when given to a phlorhizinized dog produces little or no glucose.[2] When added to a perfusing fluid and passed through a surviving liver leucin yields acetone bodies in large amounts.[3] Baer and Blum[4] found a greatly increased output of β-oxybutyric acid after giving 33.7 grams of leucin to a diabetic patient. The chemical reaction undoubtedly follows the known laws of oxidation on the α-amino group of the amino-acids of β-oxidation and cleavage of a methyl radicle whose further fate is unknown. These reactions may thus be presented:



The end-product of the metabolism of leucin is, therefore, the same as the end-product of ordinary fat metabolism.

Phenylalanin, $C_6H_5.CH_2.CHNH_2COOH$, and **Tyrosin,** $HO.C_6H_4.CH_2.CHNH_2COOH$.—*Yield β-oxybutyric acid, and in alcaptonuria homogentisic acid. Present in all proteins, except that tyrosin is absent in gelatin.*

The metabolism of these substances has already been considered in some detail (see p. 178). Embden and Baldes[5] state that when phenylalanin is added to the perfusing fluid

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[1] Dakin: "Journal of Biological Chemistry," 1913, xiv, 321.

[2] Halsey: "American Journal of Physiology," 1904, x, 229; Dakin: *Loc. cit.*

[3] Embden, Salomon, and Schmidt: *Loc. cit.*

[4] Baer and Blum: "Arch. f. ex. Path. und Pharm.," 1906, lv, 89.

[5] Embden and Baldes: "Biochemische Zeitschrift," 1913, lv, 301.

passing through the liver it may be converted into tyrosin. Even though phenylalanin does not always yield tyrosin in the organism, yet it is believed that it may be converted into p-oxyphenylpyruvic acid, which is the first oxidation product of tyrosin.

In the phenomenon called *alcaptonuria* (see p. 178), tyrosin and phenylalanin are believed to be oxidized only as far as *homogentisic acid*, in which form they appear in the urine. Falta[1] reports that if phenylalanin or tyrosin be administered in alcaptonuria each is completely converted into homogentisic acid and so eliminated. In alcaptonuria the ratio between homogentisic acid and nitrogen elimination in the urine is quite constant, being 45 : 100 or 50 : 100,[2] and the distribution of the various other nitrogenous compounds in the urine remains normal.

Neubauer and Falta[3] emphasized the idea that homogentisic acid is always formed in normal metabolism, but in this rare disease cannot be oxidized. The power to split the benzol ring was absent.

However, Dakin[4] has administered to alcaptonurics paramethylphenylalanin, $CH_3.C_6H_4.CH_2CHNH_2COOH$, and paramethoxyphenylalanin, $CH_3O.C_6H_4.CH_2CHNH_2COOH$, substances which cannot undergo the quinoid transformation, (see p. 178) and has found that these are oxidized in the organism. He, therefore, concludes that the formation of homogentisic acid in metabolism is always pathologic, and that the benzol ring can be broken even in alcaptonuria without its intermediation. Fromherz and Hermanns[5] believe that the aromatic amino-acids normally follow a dual path to

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[1] Falta: "Biochemisches Centralblatt," 1904–05, iii, 175.

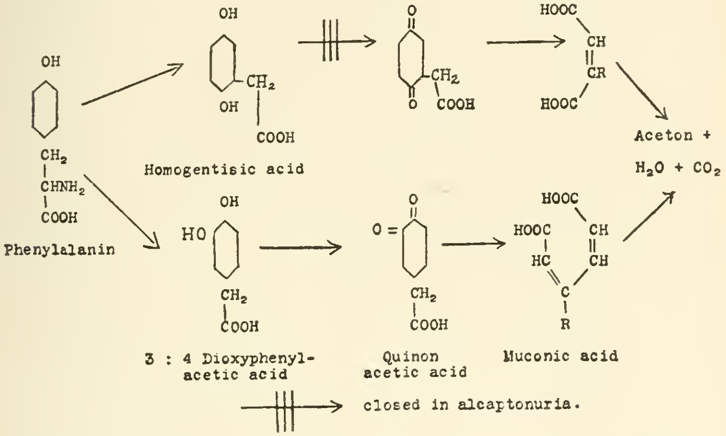
[2] Langstein and Meyer: "Deutsches Archiv für klinische Medizin," 1903, lxxviii, 161; Schumm: "Münchener med. Wochenschrift," 1904, li, 1599; Garrod and Hele: "Journal of Physiology," 1905, xxxiii, 205; Ravold and Warren: "Journal of Biological Chemistry," 1909–10, vii, 465.

[3] Neubauer and Falta: "Zeitschrift für physiologische Chemie," 1904, xlii, 81.

[4] Dakin: "Journal of Biological Chemistry," 1911, ix, 151.

[5] Fromherz and Hermanns: "Zeitschrift für physiologische Chemie," 1914, xci, 194.

destruction and that one of these is closed in alcaptonuria, whereas the other remains open. They present this picture of the process:



It will be recalled that muconic acid has been considered as representing the opening door of the benzol ring, ever since Jaffé[1] gave benzol to a rabbit and found muconic acid in the urine.

Phenylalanin, tyrosin, homogentisic acid,[2] and muconic acid[3] all yield acetone bodies when perfused through a surviving liver.

The reaction involving the production of β-oxybutyric acid cannot yet be written, though two of its four carbon atoms are probably derived from the phenyl ring and two from the side chain.[4]

Tyrosin yields no sugar in the phlorhizinized dog,[5] nor does phenylalanin.[6]

When the ammonium salts of the keto-acids corresponding to phenylalanin and tyrosin are perfused through a surviving

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[1] Jaffé: "Zeitschrift für physiologische Chemie," 1909, lxii, 58.

[2] Embden, Salomon, and Schmidt: *Loc. cit.*

[3] Hensel and Riesser: "Zeitschrift für physiologische Chemie," 1913, lxxxviii, 38.

[4] Wakeman and Dakin: "Journal of Biological Chemistry," 1911, ix, 139.

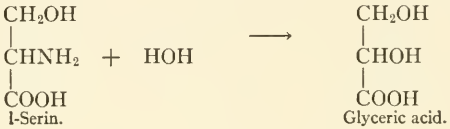
[5] Ringer and Lusk: *Loc. cit.;* confirmed by Dakin.

[6] Dakin: "Journal of Biological Chemistry," 1913, xiv, 321.

liver there may be a synthetic production of the two last-named substances.[1] The reaction of deamination is, therefore, reversible in these cases.

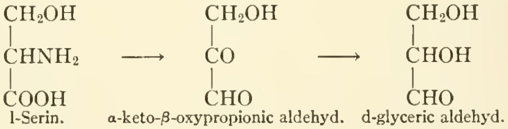
l-Serin, $CH_2OH.CHNH_2COOH$.—*Detected in small quantities in many proteins. Three carbon atoms are able to enter into the formation of glucose.*

Dakin[2] showed that the ingestion of 11.9 grams of serin by a phlorhizinized dog resulted in the excretion of 11 grams of extra glucose in the urine. One might picture the conversion of serin into glyceric acid which Ringer and Lusk (p. 193) showed is transformed into glucose:

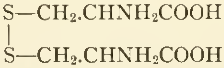


$$\begin{array}{l}CH_2OH\\ |\\ CHNH_2\\ |\\ COOH\\ \text{l-Serin.}\end{array} + HOH \longrightarrow \begin{array}{l}CH_2OH\\ |\\ CHOH\\ |\\ COOH\\ \text{Glyceric acid.}\end{array}$$

But in order to remove the asymmetry of the central carbon atom it seems more probable that a keto-body is an intermediary oxidative product. The transformation might take the following form:



$$\begin{array}{l}CH_2OH\\ |\\ CHNH_2\\ |\\ COOH\\ \text{l-Serin.}\end{array} \longrightarrow \begin{array}{l}CH_2OH\\ |\\ CO\\ |\\ CHO\\ \text{a-keto-}\beta\text{-oxypropionic aldehyd.}\end{array} \longrightarrow \begin{array}{l}CH_2OH\\ |\\ CHOH\\ |\\ CHO\\ \text{d-glyceric aldehyd.}\end{array}$$

Cystin, 

$$\begin{array}{l}S—CH_2.CHNH_2COOH.\\ |\\ S—CH_2.CHNH_2COOH\end{array}$$

—*Present in most proteins. Six carbon atoms probably may enter into the formation of glucose.*

In a rare disease called cystinuria cystin appears dissolved in the urine, or it may take the form of stone or of sediment. If cystin be administered to a normal person it is oxidized, and does not alter the normal relation between oxidized and unoxidized sulphur in the urine.[3] If cystin be given to a patient with cystinuria a part is eliminated, but a still greater

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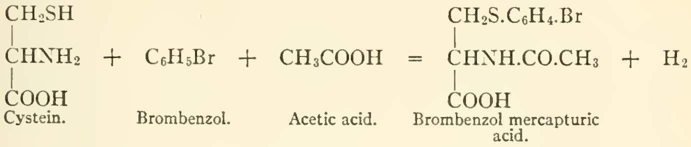
[1] Embden and Schmitz: "Biochemische Zeitschrift," 1910, xxix, 423,

[2] Dakin: *Loc. cit.*

[3] Blum: "Hofmeister's Beitrage," 1904, v, 1.

part is oxidized.[1] The disturbance, therefore, is not complete. When protein is given in increased measure the cystin elimination is increased in the cystinuric patient.[2] The increase in neutral sulphur found in the urine is at the expense of the alkaline sulphate usually found there.

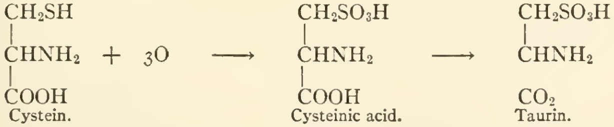
In normal metabolism cystin is probably first broken up into two molecules of cystein, for on giving brombenzol *mercapturic acid* appears in the urine. This acid is a compound of cystein, brombenzol, and acetic acid. The reaction, as shown by Friedmann,[3] takes place as follows:



$$\underset{\text{Cystein.}}{\begin{array}{l}CH_2SH\\ |\\ CHNH_2\\ |\\ COOH\end{array}} + \underset{\text{Brombenzol.}}{C_6H_5Br} + \underset{\text{Acetic acid.}}{CH_3COOH} = \underset{\text{Brombenzol mercapturic acid.}}{\begin{array}{l}CH_2S.C_6H_4.Br\\ |\\ CHNH.CO.CH_3\\ |\\ COOH\end{array}} + H_2$$

This affords an example of *acetylation* not uncommon in the organism.[4] Acetic acid is probably constantly available, being derived from the metabolism of fat (see p. 302).

Marriott and Wolf[5] further investigated this condition of artificially induced cystinuria, and were able to increase the unoxidized sulphur (cystein-S) in the urine fourfold by this means, and nearly to remove all the oxidized sulphur. The sulphur was, therefore, not oxidized to sulphate as in the normal state. That cystein is the mother substance of the taurin of the bile Friedmann[6] illustrates in accordance with the following formula:



$$\underset{\text{Cystein.}}{\begin{array}{l}CH_2SH\\ |\\ CHNH_2\\ |\\ COOH\end{array}} + 3O \longrightarrow \underset{\text{Cysteinic acid.}}{\begin{array}{l}CH_2SO_3H\\ |\\ CHNH_2\\ |\\ COOH\end{array}} \longrightarrow \underset{\text{Taurin.}}{\begin{array}{l}CH_2SO_3H\\ |\\ CHNH_2\\ \\ CO_2\end{array}}$$

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[1] Williams and Wolf: "Journal of Biological Chemistry," 1909, vi, 337.

[2] Alsberg and Folin: "American Journal of Physiology," 1905, xiv, 54.

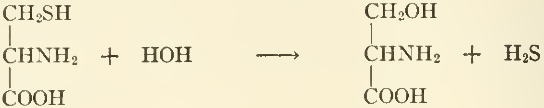
[3] Friedmann: "Hofmeister's Beitrage," 1904, iv, 486.

[4] Consult von Fürth: "Probleme der physiologischen und pathologischen Chemie," Leipzig, 1913, ii, p. 465.

[5] Marriott and Wolf: "American Medicine," 1905, ix, 1026. See also Zeller and Straczewski: "Archiv für Physiologie," 1914, p. 585.

[6] Friedmann: "Hofmeister's Beiträge," 1903, iii, 1.

Taurin, however, is not the only pathway of cystein destruction, for Dakin[1] gave a phlorhizinized dog 15.7 grams of cystein, which theoretically is convertible into at most 11.6 grams of glucose, and found 12.2 grams of extra glucose in the urine. This transformation would be conceivable through hydrolysis and the conversion of cystein into serin, which, as already stated, is convertible into glucose.



$$\begin{array}{l}CH_2SH\\ |\\ CHNH_2\\ |\\ COOH\end{array} + HOH \longrightarrow \begin{array}{l}CH_2OH\\ |\\ CHNH_2\\ |\\ COOH\end{array} + H_2S$$

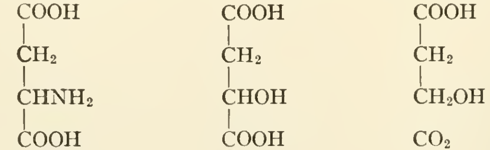
Cystein. Serin.

Dakin made note of the fact that the sulphur excretion under the conditions of his experiments was in the form of sulphate and was relatively very slow. This is contrary to the usual behavior of the sulphur contained in cystein (see p. 168).

It is evident that cystein metabolism has the choice of at least two different pathways in the organism.

Aspartic Acid, $HOOC.CH_2.CHNH_2.COOH$.—*Present in most proteins. Three carbon atoms enter into the formation of glucose.*

Aspartic acid was given to phlorhizinized dogs by Ringer and Lusk[2] and the equivalent of three carbon atoms was recovered as glucose in the urine. This has been confirmed in Cremer's laboratory by Hering,[3] who administered asparagin. The possible pathways of this transformation are several. Ringer and Lusk gave the following course:



$$\begin{array}{l}COOH\\ |\\ CH_2\\ |\\ CHNH_2\\ |\\ COOH\end{array} \qquad \begin{array}{l}COOH\\ |\\ CH_2\\ |\\ CHOH\\ |\\ COOH\end{array} \qquad \begin{array}{l}COOH\\ |\\ CH_2\\ |\\ CH_2OH\\ \\ CO_2\end{array}$$

Aspartic acid. Malic acid. β-Lactic acid.

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[1] Dakin: *Loc. cit.*

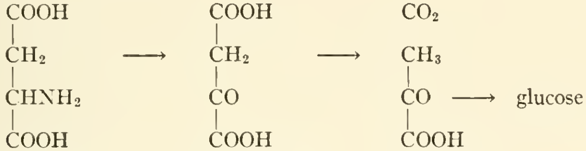
[2] Ringer and Lusk: *Loc. cit.*

[3] Hering: "Cremer's Beiträge zur Physiologie," 1914, i, 1.

Later Ringer[1] found that malic acid was in large measure convertible into glucose.

This conception of intermediary reaction is supported by the finding of Ackermann[2] that digestion of aspartic acid with putrid pancreas produces β-alanin, $H_2NCH_2.CH_2.COOH$.

Dakin[3] considers that alanin or lactic acid are the primary cleavage products of aspartic acid metabolism, and this is attested by the researches of Meyer[4] in Neuberg's laboratory, who finds that tissue pulp of liver and muscle convert keto-succinic acid into pyruvic acid. The reaction would then take place as follows:



$$\begin{array}{lclcll} COOH & & COOH & & CO_2 & \\ | & & | & & & \\ CH_2 & \longrightarrow & CH_2 & \longrightarrow & CH_3 & \\ | & & | & & | & \\ CHNH_2 & & CO & & CO & \longrightarrow \text{glucose} \\ | & & | & & | & \\ COOH & & COOH & & COOH & \end{array}$$

Aspartic acid. Keto-succinic acid. Pyruvic acid.

One, or perhaps both, of these pathways are open in the organism for the metabolism of aspartic acid and for synthesis of glucose from it should conditions favor.

Glutamic Acid, $HOOC.CH_2.CH_2.CHNH_2.COOH$.—*Present in all proteins, frequently largest constituent amino-acid in the molecule, as in gliadin of wheat (44 per cent.) and in muscle (22 per cent.). Three carbon atoms enter into the formation of glucose.*

This was the first amino-acid whose power to form glucose was measured.[5] Ringer and Lusk held that this power to form glucose was through β-oxidation of the central carbon atom, as follows:

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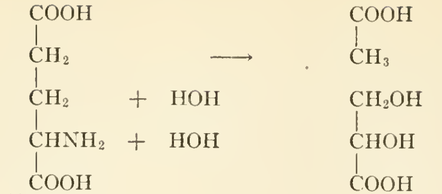
[1] Ringer, Frankel, and Jonas: "Journal of Biological Chemistry," 1913, xiv, 539.

[2] Ackermann: "Zeitschrift für Biologie," 1911, lvi, 87.

[3] Dakin: *Loc. cit.*

[4] Mayer, P.: "Biochemische Zeitschrift," 1914, lxii, 462.

[5] Lusk: "American Journal of Physiology," 1908, xxii, 174.



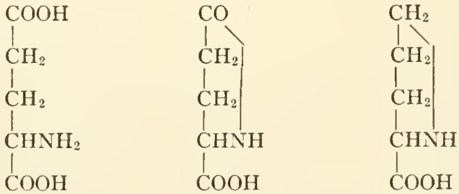
$$\begin{array}{l}\mathrm{COOH}\\ |\\ \mathrm{CH_2}\\ |\\ \mathrm{CH_2} + \mathrm{HOH}\\ |\\ \mathrm{CHNH_2} + \mathrm{HOH}\\ |\\ \mathrm{COOH}\end{array} \longrightarrow \begin{array}{l}\mathrm{COOH}\\ |\\ \mathrm{CH_3}\\ \\ \mathrm{CH_2OH}\\ |\\ \mathrm{CHOH}\\ |\\ \mathrm{COOH}\end{array}$$

Glutamic acid. Glyceric acid.

Since glyceric acid forms glucose, this pathway would be a natural one. Dakin agrees with this as possible. Warkalla[1] confirms the synthesis of three carbon groups of glutamic acid into glucose.

F. Ehrlich[2] showed that fermenting yeast converted glutamic acid into succinic acid, $HOOC.CH_2.CH_2.COOH$, and Neuberg[3] finds that keto-glutaric acid, $HOOC.CH_2.CH_2.CO.-COOH$, yields the same product under similar conditions. This indicates keto-glutaric acid as a probable intermediary product. Since Ringer[4] has shown that succinic acid is convertible into glucose, this appears to be a possible pathway of the decomposition of glutamic acid.

According to Abderhalden,[5] glutamic acid may be condensed into pyrrolidon carboxylic acid. The conversion of this into prolin or pyrrolidin carboxylic acid has not yet been achieved.



Glutamic acid. Pyrrolidon carboxylic acid. Pyrrolidin carboxylic acid.

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[1] Warkalla: "Cremer's Beiträge," 1914, i, 91.

[2] Ehrlich, F.: "Biochemische Zeitschrift," 1909, xviii, 391.

[3] Neuberg and Ringer, M.: *Ibid.*, 1915, lxxi, 226.

[4] Ringer, Frankel, and Jonas: "Journal of Biological Chemistry," 1913, xiv, 539.

[5] Abderhalden and Kautzsch: "Zeitschrift für physiologische Chemie," 1910, lxviii, 487.

Pyrrolidin carboxylic acid made in some such manner may become the mother substance used in the construction of hemoglobin in the animal or of chlorophyll in the plant.

Lysin, $NH_2.CH_2.CH_2.CH_2.CH_2.CHNH_2.COOH$.—*Present in proteins of animal origin. Absent in zein and present in very small amount in such a vegetable protein as gliadin. It is the only amino-acid with a straight chain which does not form glucose.*

Dakin[1] gave lysin to a phlorhizinized dog, but found neither extra sugar nor an increase in the β-oxybutyric acid excretion in the urine. This is explained by Ringer[2] on the ground that lysin may be converted into glutaric acid, $HOOC.C_3H_6.COOH$, which does not form glucose when administered in phlorhizin glycosuria.[3] The small increase in β-oxybutyric acid elimination noted by Ringer in this experiment does not necessarily indicate that this substance is an intermediary metabolism product.

The oxidation to COOH of the ε-C, to which an NH_2 group is attached, followed by β-oxidation, would yield aspartic acid, provided the NH_2 in the ε-position remained untouched. Such a course of metabolism would cause lysin to yield glucose in abundance and is therefore excluded.

Bacteria in intestinal putrefaction convert lysin into cadaverin, $NH_2—C_5H_{10}—NH_2$, through simple CO_2 cleavage. In severe cases of cystinuria the diamines cadaverin and putresin (see p. 204) appear in the urine and this constitutes diaminuria.[4]

Arginin, $NH_2.CNHNH.CH_2CH_2CH_2.CHNH_2.COOH$.—*Present in most proteins. Probably three carbon atoms form glucose.*

Kossel and Dakin[5] found that liver but not muscle con-

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[1] Dakin: *Loc. cit.*

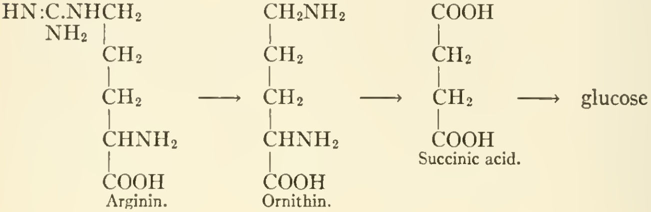
[2] Ringer, Frankel, and Jonas: *Loc. cit.*

[3] Ringer: "Journal of Biological Chemistry," 1912, xii, 223.

[4] Literature, v. Fürth: "Probleme der physiologischen und pathologischen Chemie," 1913, Bd. II, p. 117.

[5] Kossel and Dakin: "Zeitschrift für physiologische Chemie," 1904, xli, 321; 1904, xlii, 183.

tained an enzyme capable of splitting d-arginin into urea and ornithin, the only reaction by which urea is obtained as a simple cleavage product of an amino-acid. Dakin[1] gave both arginin and ornithin to a phlorhizinized dog, and witnessed a sufficient elimination of extra glucose to account for three of the carbon atoms in these substances. Since three carbon atoms of succinic acid enter into the formation of glucose, and succinic acid appears to be a possible product of the metabolism of ornithin, one may assume that this might represent the pathway into sugar. These formulæ may thus be portrayed:



$$\underset{\text{Arginin.}}{HN{:}C(NH_2).NHCH_2.CH_2.CH_2.CHNH_2.COOH} \longrightarrow \underset{\text{Ornithin.}}{CH_2NH_2.CH_2.CH_2.CHNH_2.COOH} \longrightarrow \underset{\text{Succinic acid.}}{COOH.CH_2.CH_2.COOH} \longrightarrow \text{glucose}$$

Another possible pathway would be the oxidation of the δ-C atom of ornithin to COOH, with the production of glutamic acid, which would then break up with sugar formation (see p. 201).

Bacteria in the intestine may convert ornithin into *putresin*, $NH_2—C_4H_8—NH_2$, through the cleavage of CO_2 (see p. 203).

Arginin is the only amino-acid containing the guanidin nucleus, which is also found in creatin. However, attempts to associate the origin of creatin from arginin have proved fruitless. Jaffé[2] gave nitrate of arginin subcutaneously to a rabbit, but found no change in the amount of creatin in the urine or muscle. According to the known laws of oxidation of amino-acids, guanidin acetic acid, $NH_2.CNH.NH.CH_2.COOH$, might readily be an oxidation product of arginin. When Jaffé gave this substance to a rabbit he found that a methyl

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[1] Dakin: *Loc. cit.*

[2] Jaffé: "Zeitschrift für physiologische Chemie," 1906, xlviii, 430.

group was added and it was in part eliminated in the urine as creatin, $NH_2.CNH.NCH_3.CH_2.COOH$. The proof of the origin of guanidin acetic acid in the organism is, however, lacking. Arginase does not effect the cleavage of creatin or guanidin acetic acid[1] (see also p. 209).

Histidin, $N : CH.NH.CH : C.CH_2.CHNH_2.COOH$.—*Present in most proteins. Does not produce glucose, and there is no clear evidence that it produces β-oxybutyric acid.*

When histidin is given to dogs it is oxidized and urea formed from it appears in the urine.[2] When it is given to phlorhizinized dogs Dakin[3] finds no clear-cut evidence that it is converted either into glucose or β-oxybutyric acid.

Histidin gives Ehrlich's diazo-reaction, and is probably the chromogen within urochrom.[4]

Prolin, $NH.CH_2.CH_2.CH_2.CH.COOH$.—*Present in most proteins. Three carbon atoms enter into the formation of glucose.*

Dakin[5] gave prolin to a phlorhizinized dog and found extra glucose eliminated to the extent of three of the five carbon atoms contained in prolin. Ringer suggests that the intermediary product may be succinic acid, but lactic acid or glyceric acid are also possible. The metabolism probably follows the same lines as does that of glutamic acid (see p. 202).

Tryptophan (*Formula below*).—*Present in animal proteins except gelatin. Absent in zein. Produces neither glucose nor β-oxybutyric acid, but is convertible into kynurenic acid.*

Dakin[6] could find no certain increase in sugar or β-oxybutyric acid excretion after giving 14.5 grams of tryptophan to a phlorhizinized dog.

Ellinger[7] discovered that the production of kynurenic

[1] Dakin: "Journal of Biological Chemistry," 1907, iii, 435.

[2] Abderhalden and Einbeck: "Zeitschrift für physiologische Chemie," 1909, lxii, 322; 1910, lxviii, 395.

[3] Dakin: "Journal of Biological Chemistry," 1913, xiv, 328.

[4] von Fürth: "Probleme der physiologischen und pathologischen Chemie," 1913, ii, 605.

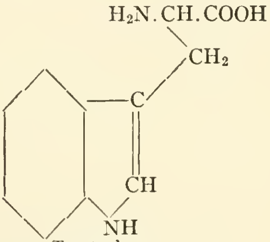
[5] Dakin: "Journal of Biological Chemistry," 1912–13, xiii, 513.

[6] Dakin: *Ibid.*, 1913, xiv, 321.

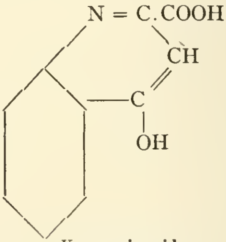
[7] Ellinger: "Zeitschrift für physiologische Chemie," 1904, xliii, 325.

acid, which had long been known as a component of dog's urine, was largely increased after giving tryptophan. Mendel and Jackson[1] found that the kynurenic acid elimination in dogs varied directly with the protein metabolism, but was not derived from gelatin metabolism. Ellinger also gave tryptophan to a rabbit, whose urine normally contains no kynurenic acid, and found kynurenic acid in the urine. Rabbits however, normally oxidize kynurenic acid when ingested in small amounts. He reaches the conclusion that animals in general may produce kynurenic acid, and that this is usually readily oxidized except in the organism of the dog, where it is only partly destroyed, and therefore appears in the urine.

Hopkins and Cole[2] first isolated tryptophan in a state of purity and determined its formula. Miss Homer[3] determined the exact formula of kynurenic acid. Ellinger[4] thus presents the transformation of tryptophan into kynurenic acid:

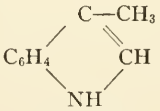


Tryptophan.
Indol aminopropionic acid.

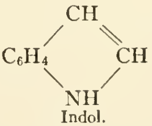


Kynurenic acid.
γ-oxy-α-quinolin carboxylic acid.

Intestinal bacteria act upon the propionic acid radicle of tryptophan and convert it into skatol or indol:



Skatol.



Indol.

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[1] Mendel and Jackson: "American Journal of Physiology," 1898–99, ii, 1.
[2] Hopkins and Cole: "Journal of Physiology," 1901–02, xxvii, 418.
[3] Homer: "Journal of Biological Chemistry," 1914, xvii, 509.
[4] Ellinger and Matsuoka: "Zeitschrift für physiologische Chemie," 1914, xci, 45.

Indol and skatol, together with phenol, $C_6H_5.OH$, and p-cresol, $CH_3.C_6H_4.OH$, the products of bacterial putrefaction of phenylalanin and tyrosin, are conjugated with sulphuric acid in the liver and are eliminated as ethereal sulphates in the urine.

Summary.—It has been noted that in completely phlorhizinized dogs the actual D : N ratio is 3.65 : 1. How accurately may one calculate the theoretic origin of glucose from the present amount of information at hand? If the analysis of muscle tissue given by Osborne (see p. 77) be taken, one may estimate how much sugar may arise from the various fragments of the protein molecule.

CALCULATION SHOWING THE ORIGIN OF GLUCOSE FROM PROTEIN

Substance.	From 100 Grams of Protein. Amino Acid. Grams.	 Glucose. Grams.
Glycocoll	4.0	3.2
Alanin	8.1	8.2
Aspartic acid	10.6	7.2
Glutamic acid	22.3	13.6
Prolin	8.0	6.3
Arginin	11.5	5.9
Cystin *	...	...
Serin *	...	...
	64.5	44.4

* Amount not given.

Since 100 grams of the ox muscle contained 16.18 grams of nitrogen and from this same material 44.4 grams of glucose may be calculated to arise, one may deduce the equation, $D : N = \frac{44.4}{16.18} = 2.75 : 1$. If the D : N ratio is 3.65, 59 gm. of glucose, or 14.6 gm. more than the quantity above estimated, are eliminated in the urine when 100 gm. of protein are destroyed. These 14.6 gm. represent an additional amount of glucose, whose origin is unexplained and which is equal to 24 per cent. of the total maximal production. Such sources of sugar might be cystin, which, if all the sulphur in protein were in that form, might at most yield 2 grams of glucose, serin whose solubility prevents accuracy of determination, and glycocoll formed synthetically.

Though the analytic methods are admittedly crude, yet they give some insight into the possibilities of transformation of a heterogeneous medley of amino-acids into a common substance, glucose, the carbohydrate of the organism.[1]

Leucin, tyrosin, and phenylalanin, on the other hand, yield β-oxybutyric acid, or the end-product characteristic of fat metabolism, whereas the final products of valin, lysin, histidin, and tryptophan are unknown.

ADDENDUM CONCERNING THE COMPOSITION OF THE URINE

The urine removes the soluble products of metabolism from the organism and the respiration eliminates the gaseous products. The two mechanisms combined maintain the normal reaction of the blood.

In general, the organic constituents of the urine comprise compounds which contain nitrogen. Dakin,[2] however, finds that formic acid, H.COOH, is a constant constituent of urine during fasting, and that the quantity is considerably increased after carbohydrate and after fat ingestion, to a lesser extent also after protein ingestion. He interprets this as signifying that all three foodstuffs yield formic acid as an end-product of their metabolisms. Although the production of formic acid may be considerable, it is so readily oxidizable that it is eliminated in only small amounts in the urine.

The study of creatinin and creatin as excretory products was stimulated by the discovery by Folin of a quick and accurate method of determination.

He gave a diet of milk, cream, and carbohydrate which is free from creatinin and the purin bases, and noted the effect of high and low protein content of the diet on the composition of human urine.

One of Folin's[3] experiments may thus be tabulated, percentages being rendered in black type (see Appendix, p. 573):

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[1] Further details, Lusk: "Archives of Internal Medicine," 1915, xv, 939.

[2] Dakin, Janney, and Wakeman: "Journal of Biological Chemistry," 1913, xiv, 341.

[3] Folin: "American Journal of Physiology," 1905, xiii, 117.

INFLUENCE OF HIGH AND LOW PROTEIN DIETS ON THE RELATIVE AMOUNTS OF THE NITROGENOUS CONSTITUENTS OF THE URINE.

Food.		Composition of the Urine in Grams.					
In Grams.	In Calories.	Total N.	Urea N.	Ammonia N.	Uric Acid N.	Creatinin N.	Undetermined N.
Protein, 118 = 19 N. Fat, 148 Carb., 225	2786	16.8	14.70 87.5%	0.49 3.0%	0.18 1.1%	0.58 3.6%	0.85 4.9%
Protein, 6 = 1 N. Fat, 52 Carb., 400	2153	3.6	2.20 61.7%	0.42 11.3%	0.09 2.5%	0.60 17.2%	0.27 7.3%

A study of this table will reveal the fact that if a man ingest a diet containing a medium amount of protein, and again one that is nearly free from protein, the difference in the character of the urine in the two cases is almost exclusively due to a difference in the output of urea. The quantity of creatinin eliminated remains independent of the quantity of protein metabolized, and the same thing holds true, as a rule, for uric acid (see p. 540). This led Folin to distinguish between an *endogenous* protein metabolism which resulted in the constant and even production of creatinin and was a manifestation of cell metabolism, and an *exogenous* protein metabolism as represented by the urea elimination which is in greater part derived from ingested protein.

Creatinin.—McCollum[1] has observed that pigs may be nourished for long periods of time when fed with a mixture of starch and inorganic salts in sufficient quantity to maintain their weights and energy requirements. After twenty-one to thirty-six days of this diet the relation of creatinin N to total N in the urine is a constant, or 18.5 : 100. Since the creatinin N has this as an invariable constant (when the diet is free from this constituent) it follows that the true minimal

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[1] McCollum: "American Journal of Physiology," 1911–12, xxix, 210.

endogenous level of protein metabolism may be calculated at any stage of the experiment by multiplying the quantity of creatinin N by 5.5 Nitrogen in excess of this is supposed to be derived from the destruction of "deposit protein" (see p. 287).

The table just given, which shows Folin's urinary figures for the seventh day of a starch-cream diet in man, shows a relationship of 17.2 : 100 between creatinin N and total N, thus indicating that the principle may be applicable to man.

The daily elimination of a gram or more of creatinin in the urine is certainly of moment.

Creatinin continues to be eliminated after an Eck fistula (p. 451) has been established in a dog,[1] indicating that the liver cannot be all important in its production. If creatinin be administered with the food it is almost completely eliminated in the urine.[2] The creatinin elimination is not influenced by muscular work,[3] nor by the increased metabolism of body proteins which follows phosphorus-poisoning in fasting dogs.[4]

All of these facts seem to indicate that there is a mechanism in the muscles which is constantly active preparing a definite quantity of creatinin. Whether this comes from arginin or not is unknown (see p. 204).

Shaffer[5] has proposed the term *creatinin coefficient* to represent the number of milligrams of creatinin nitrogen eliminated per kilogram of body weight in twenty-four hours. He believes this to be an index of muscular development. In 37 normal men the creatinin coefficient was between 8 and 11. In full accord with this theory Tracy and Clark[6] find the creatinin coefficient of 26 normal women students in a profes-

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[1] London and Boljarski: "Zeitschr. für physiol. Chemie," 1909, lxii, 465.

[2] Folin: "Hammarsten's Festschrift," 1906.

[3] Van Hoogenhuyze and Verploegh: "Zeitschrift für physiologische Chemie," 1905, xlvi, 415.

[4] Lusk: "American Journal of Physiology," 1907, xix, 461.

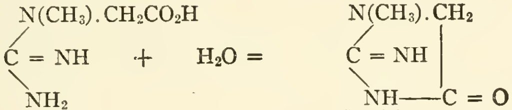
[5] Shaffer: *Ibid.*, 1908, xxiii, 1.

[6] Tracy and Clark: "Journal of Biological Chemistry," 1914, xix, 115.

sional school to average 5.8. In two athletic women, with unusual muscular development and control through gymnastic exercise, the creatinin coefficients were 9 and 9.8 or the same as in men.

Arguing from the premise that the creatinin metabolism is an index of the quantity of active protoplasm of muscle tissue, Palmer, Means, and Gamble[1] have compared the basal metabolism of 8 men and 9 women in relation to their output of creatinin. The group of men produced 0.98 calories of heat per milligram of excreted creatinin, and the group of women 1.26 calories for the same unit. If the premise is correct, then the mass of active protoplasm is not a factor in the measurement of the intensity of the basal metabolism (see p. 130).

Creatin.—Creatinin is the anhydrid of creatin, a constituent of normal muscle. Creatin by treatment with acid is converted into creatinin as follows:



Creatin. Creatinin.

The close chemical relation between these two substances has led to a search into the problem of their physiologic interrelation, which as yet has been crowned with small success.

Myers and Fine[2] report the following creatin content of muscle in various species:

Man	0.39	per cent. creatin.
Dog	0.37	" "
Cat	0.45	" "
Rabbit	0.52	" "

When creatin is administered it may be destroyed or eliminated in the urine, but it is not eliminated as creatinin.

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[1] Palmer, Means, and Gamble: "Journal of Biological Chemistry," 1914, xix, 239.

[2] Myers and Fine: *Ibid.*, 1913, xiv, 9.

Folin[1] and F. G. Benedict[2] first reported the presence of creatin in the urine of fasting men and offered the hypothesis that it arose from disintegrating muscle tissue. Cathcart[3] independently made the same observation, but witnessed the disappearance of creatin from the urine of the fasting man after giving him carbohydrate, and first suggested that carbohydrate metabolism was associated with creatin oxidation. Mendel and Rose[4] reached the same conclusion.

The appearance of creatin in .the urine in various other conditions has been attributed to the elimination of creatin liberated through muscle breakdown, but may now be explained as due to lack of carbohydrate metabolism. Among the conditions reported in which creatin appears in the urine are phosphorus-poisoning,[5] carcinoma of the liver,[6] during the period of the involution of the uterus after parturition[7] and also immediately before parturition.[8]

However, Mellanby[9] has shown that cesarean section with removal of the uterus is followed by the same excretion of creatin as after normal parturition. Morse[10] confirms these observations.

That creatin elimination is not an index of cellular destruction was beautifully shown by Stanley Benedict,[11] who maintained a phlorhizinized and fasting dog nearly in nitrogen and weight equilibrium by feeding him with washed meat. The results are given below:

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[1] Folin: "Hammarsten's Festschrift," 1906.

[2] Benedict, F. G.: Carnegie Institution of Washington, 1907, Publication No. 77, p. 386.

[3] Cathcart: "Journal of Physiology," 1907, xxxv, 500.

[4] Mendel and Rose: "Journal of Biological Chemistry," 1911–12, x, 213.

[5] Lefmann: "Zeitschrift für physiologische Chemie," 1908, lvii, 476.

[6] Van Hoogenhuyze and Verploegh: *Ibid.*, 1908, lvii, 161. Also Mellanby, "Journal of Physiology," 1908, xxxvi, 447.

[7] Shaffer: "American Journal of Physiology," 1908, xxiii, 14.

[8] Murlin: *Ibid.*, 1909, xxiii, p. xxxi.

[9] Mellanby, E.: Proc. of the Royal Society, London, Series B, 1912, lxxvi, 88.

[10] Morse, A.: "Journal of the Amer. Med. Assoc.," 1915, lxv, 1613.

[11] Benedict, S. R., and Osterberg: "Journal of Biological Chemistry," 1914, xviii, 195.

CREATIN EXCRETION IN A PHLORHIZINIZED DOG IN N EQUILIBRIUM

	Weight.	N in Food.	N in Urine.	N Loss From Body.	Creatin N.	Creatinin N.	D : N.
	Kg.	Grams.	Grams.	Grams.	Grams.	Grams.	
Third day fasting	7.62	.....	2.74	−2.74	0.075	0.075	
Fourth day fasting: phlorhizin.	7.58	.....	6.34	−6.34	0.110	0.074	3.9
Second day phlorhizin.........	7.44	12.00	11.91	−1.21	0.154	0.071	3.4
Fifth day phlorhizin.........	7.08	13.46	12.79	−1.23	0.131	0.070	3.2

On account of the maintenance of the quantity of body protein the creatinin excretion remained constant, but in spite of this maintenance there was a large elimination of creatin. At the completion of the experiments analysis of the muscle-cells showed more rather than less than the normal content of creatin. These are the only experiments which demonstrate an elimination of creatin without a corresponding loss of body tissue or loss of muscle creatin. Stanley Benedict concludes that the creatin elimination is due to complete carbohydrate starvation, that under normal conditions creatin is probably formed in the organism in relatively large amounts, and is for the most part utilized or destroyed when carbohydrate is being oxidized as well.

A long-continued carbohydrate diet which is free from protein reduces the quantity of creatin present in muscle tissue.[1]

Muscular fatigue leaves the creatin content of dog's muscle unchanged from the normal.[2]

Summarizing the known data, it appears that creatinin is not oxidized in the organism, but if formed is probably completely eliminated in the urine, whereas creatin is continuously produced in quantities above the requirement for the saturation of muscle tissue, and this excess in the presence of carbo-

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[1] Myers and Fine: "Journal of Biological Chemistry," 1913, xv, 305.

[2] Mellanby: "Journal of Physiology," 1908, xxxvi, 447; Scaffidi: "Biochemische Zeitschrift," 1913, l, 402.

hydrate oxidation may be destroyed, but in the case of carbohydrate starvation may be eliminated in the urine.

Uric Acid.—See Chapter on Purin Metabolism.

THE REACTION OF URINE AND BLOOD

Ammonia.—Friedrich von Müller[1] was the first to affirm that the number of grams of ammonia eliminated by an organism during twenty-four hours might be used as an indicator of the intensity of acid formation within the body. Infection of the bladder leading to ammoniacal fermentation has sometimes caused erroneous deductions to be drawn from experimental data. Murlin and Bailey[2] found that the bladder, especially in women, could be irrigated to advantage with a warm saturated solution of boric acid in order to avoid this complication.

To understand the conditions under which ammonia appears in the urine, one must understand the mechanism by which the blood is constantly held at a point the very slightest degree on the alkaline side of neutrality.

Distilled water is absolutely neutral in reaction, that is to say, the number of free $\overset{+}{H}$ ions is equal to the number of free hydroxyl ions $\overset{-}{OH}$.[3] A normal solution of hydrochloric acid contains 1 gram of free hydrogen ions in a liter of water, whereas in pure distilled water only one-ten-millionth of a gram of free hydrogen ions is present. Solutions are acid which have more than one-ten-millionth of a gram of hydrogen ions in a liter. They become alkaline when the hydrogen ion concentration falls below this point, which for convenience may be written 10^{-7}. Thus, when the hydrogen ion concentration is one part in one hundred million or 10^{-8} the hydroxyl concentration represents one-millionth normal alkaline solution. The hydrogen ion concentration of the blood varies between 10^{-7} (which it reaches only in severe acidosis) and 10^{-8}, which is attained only after the administration of alkalies.

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[1] Müller: "von Leyden's Handbuch der Ernährungstherapie," 1903, i, 261.
[2] Murlin and Bailey: "Archives of Internal Medicine," 1913, xii, 288.
[3] Consult Michaelis: "Die Wasserstoffionenkonzentration," Berlin, 1914.

The addition of one-millionth of a gram of hydrogen ions (which would be contained in 36.5-millionths of a gram of hydrochloric acid) to a liter of water would change its hydrogen ion concentration of 10^{-7} to one of less than 10^{-6}. Some cells cannot live in this concentration of acid.

In order to abolish cumbersome numbers, such as 0.35×10^{-7}, Sörensen suggested that the negative exponent be used as a whole number. This is called the hydrogen ion exponent or P_H.

$N/10$ acid $= 10^{-1}$ $\qquad P_H = 1$

$N/1{,}000{,}000 = 10^{-6}$ $\qquad P_H = 6$

$N/500{,}000 = 2 \times 10^{-6}$ $\qquad P_H = 5.70$

$(\log. 2 = 0.3; \qquad -6 + 0.3 = -5.70)$

$N/28{,}580{,}000 = 0.35 \times 10^{-7}$ $\qquad P_H = 7.45$

The last figure given above represents an alkaline solution of three ten-millionths normal, or the equivalent of 0.000012 grams of NaOH dissolved in a liter of water. This is the usual alkalinity of the blood, and though so slight that it may almost be called neutrality is yet of definite importance.

McClendon,[1] after careful experimentation, concludes that the normal P_H of venous blood is 7.5, with a range between 7.45 to 7.55. The extreme difficulty of the technic renders the reports of many experimenters only relatively accurate.

The use of logarithms as expressive of acidity requires a little practice to accustom oneself to think, for example, that $P_H = 5.70$ represents a solution whose acidity is half that represented by $P_H = 6$. Also, it must be remembered that the smaller the figure, the higher the concentration of hydrogen ions.

To Lawrence J. Henderson[2] belongs the credit of the following analysis: The proper action of physiologic processes de-

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[1] McClendon and Magoon: "Journal of Biological Chemistry," 1916, xxv, 669.

[2] Henderson, L. J.: "Ergebnisse der Physiologie," 1909, viii, 254; "Journal of Biological Chemistry," 1911, ix, 403.

pends on the accurate adjustment and preservation of temperature, molecular concentration, and neutrality. Within the organism there is a constant formation of acid substances, principally carbonic, sulphuric, and phosphoric acids, which immediately combine either wholly or in part, according to their several avidities, with the basic constituents of the protoplasm and blood. In pathologic conditions β-oxybutyric acid and aceto-acetic acid claim their share of base. Metabolism, therefore, operates to lower the unvarying alkaline reaction of the blood. This reaction, according to Henderson, is maintained under conditions in which 89 per cent. of the phosphates of the blood are dibasic, as in Na_2HPO_4, and 11 per cent. monobasic, as NaH_2PO_4; and in which 93 per cent. of the carbon dioxid is present as in $NaHCO_3$, and 7 per cent. free as free CO_2. Henderson states that the arrangement of these four substances in the blood is such that the whole system surpasses in efficiency any possible closed aqueous solution of like concentration for preserving the hydrogen ion concentration of the blood at the normal of 0.3×10^{-7}.

If an acid be introduced into this system, not only may monosodic phosphate be formed from disodic phosphate or additional amounts of CO_2 dissociated from sodic bicarbonate, but both these acid substances may be eliminated by the kidney and lungs respectively, thereby maintaining the reaction at a normal level. The high diffusibility of these acid products assists in this regulation.

If alkali increases in the system, this though converted into bicarbonate must necessarily be accompanied by a large increase in osmotic pressure. The elimination of an alkaline urine corrects this.

Carbonic acid is lost through the lungs without loss of alkali to the body.

Phosphoric and sulphuric acids are removed from the blood by the kidney in the forms of NaH_2PO_4 and Na_2SO_4. If they were removed in other forms the urine would be intensely acid. The ordinary acid formation in the human organism corresponds to between 600 and 700 c.c. of N/10 acid solution daily.[1] On account of the bases in combination the actual P_H in 222 specimens of urines for twenty-four hours from 16 individuals showed an average value of 5.98, the range being between 5.1 to 7.[2] For a short period the urine may be as alkaline as 7.4. Blatherwick[3] finds the average P_H of 30 urines of vegetarians to be 6.63. The *titratible acidity* appears to be a function of the ionized hydrogen present, and is almost wholly due to the excess of primary phosphate over secondary phosphate.

The quantity of ammonia, though it presents a clear gain of so much alkali for the body, does not appear to vary for purposes of regulating the reaction of the blood. The main regulation is accomplished by the elimination of acid phosphate and carbon dioxid. Only in pathologic conditions with acid formation is ammonia drawn upon for purposes of regulation.

The body's reserves of alkali are considerable, and replenishment is usually accomplished through alkalis contained in the food (see p. 361).

According to Michaelis,[4] the reaction of the fluid which may be expressed from fresh tissues and thrown in boiling water to prevent postmortal acid formation is not alkaline like blood, but is almost exactly neutral.

Bearing in mind the fundamental factors presented above, one may now consider the actual results of administering acids or alkalies upon the composition of the urine and blood.

In the first place, it was shown by Haldane and Priestley[5] that a very small increase in the tension of carbon dioxid in the alveolar air was accompanied by a stimulation of the respiratory center. Krogh and Krogh[6] proved that the tension

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[1] Henderson, L. J., and Palmer: "Journal of Biological Chemistry," 1913, xiv, 81.

[2] Henderson and Palmer: *Ibid.*, 1914, xvii, 305.

[3] Blatherwick: *Ibid.*, 1914, xvii, p. xl.

[4] Michaelis and Kramsztyk: "Biochemische Zeitschrift," 1914, lxii, 180.

[5] Haldane and Priestley: "Journal of Physiology," 1905, xxxii, 225.

[6] Krogh and Krogh: "Skan. Archiv für Physiologie," 1910, xxiii, 179.

of carbon dioxid in the alveoli closely follows that of arterial blood. Finally, Hasselbalch[1] showed that in reality an increase in the hydrogen ion concentration of the blood was the real stimulus to respiration, and thus caused the blood to be automatically relieved of excess of acid ions existing in the form of $\overline{HCO_3}$. In experiments he showed that when an acid urine was being secreted the CO_2 tension of the alveolar air was lowered, indicating increased acid in the blood. A diet which produced a less acid or an alkaline urine increased the CO_2 tension of the alveolar air, indicating a larger content of alkali in the blood.

The figures for one experiment may be here reproduced:

	Alveolar CO_2 Tension in Mm. Hg.	P_H of Blood—	
		At 40 Mm. CO_2 Tension.	At Alveolar CO_2 Tension.
Meat diet...............	38.9	7·33	7·34
Vegetarian diet..........	43·3	7·42	7·36

In another experiment a larger volume of respiration was found to accompany the lower alveolar CO_2 tension, as follows:

	Alveolar CO_2 Tension in Mm. Hg.	Alveolar Ventilation Liters per Minute at 37 Degrees.
Meat diet.........................	38.5	4.40
Vegetarian diet....................	43.1	4.08

These results demonstrate that CO_2 acts only indirectly upon the respiratory center. For the maintenance of a constant reaction of the blood, more CO_2 is required in the presence of alkali than in the presence of acid. The variation in the ventilation of the lungs, brought about by the sensitiveness of the respiratory center to H ions controls the CO_2 tension in

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[1] Hasselbalch: "Biochemische Zeitschrift," 1912, xlvi, 403.

the alveoli, so that the reaction of the blood remains practically unchanged under the two given different dietary conditions.

It is only in exceptional cases that in the normal life of a man at rest the diurnal variation in the carbon dioxid tension of the alveoli exceeds the equivalent of 2 mm. of mercury.[1]

The administration of acid to such an extent that the reaction of the blood becomes acid produces death. Such blood cannot combine with carbon dioxid. Thus, after giving 90 c.c. of half-normal hydrochloric acid intravenously to a dog, death resulted in virtue of the production of an experimental acidosis, the P_H equalling 6.9 in the blood.[2] The reduction of carbonic acid in the blood of a rabbit from 45 volumes per cent. to 10.1 per cent., with accompanying dyspnea, was observed by Loewy and Münzer[3] after the administration of 0.72 gram of hydrochloric acid per kilogram of body weight, and Porges[4] has noted that intravenous injection of monosodic phosphate into a narcotized rabbit raises the respiratory quotient from 0.68 to 0.79, indicating the elimination of carbon dioxid from the plasma.

If, however, acid in moderate quantity is given with food, increased ammonia production may neutralize the acid given.

This has been beautifully shown with calves,[5] as appears in the following experiment:

CALF: WEIGHT, 100 KG.; FOOD, 9.1 KG. OF MILK DAILY

Period.	No. of Days.	N in Food.	N in Urine.	Per Cent. NN_3—N.	Per Cent. Urea N.
		Grams.	Grams.		
No acid given	9	30.00	12.4	12.8	76.0
220 c.c. normal HCl	6	30.00	12.4	19.4	74.1
330 c.c. normal HCl	7	30.00	11.5	31.7	55.8
500 c.c. normal HCl	3	30.00	12.9	37.0	43.1

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[1] Erdt: "Deutsches Archiv für klinische Medizin," 1915, cxvii, 497; Higgins, "American Journal of Physiology," 1914, xxxiv, 114.

[2] Levy, Rowntree, and Marriott: "Archives of Internal Medicine," 1915, xvi, 389.

[3] Loewy and Münzer: "Archiv für Physiologie," 1901, 81.

[4] Porges: "Biochemische Zeitschrift," 1912, xlvi, 1.

[5] Steenbock, Nelson, and Hart: "Journal of Biological Chemistry," 1914, xix, 399.

Only when the larger quantities of acid were administered did it appear that the bones were attacked, and this was at the expense of their calcium carbonate content. The administration of acid did not prevent the growth and development of the calf.

In man hydrochloric acid may be given with a similar protective rise of ammonia, as appears below:[1]

CONSEQUENCE OF ADDING HYDROCHLORIC ACID TO THE DIET OF MAN. DAILY AVERAGES

	No. of Days.	Alveolar Tension Per Cent.		Urine.			
		CO_2.	O_2.	N.	NH_3.	P_2O_5.	Cl.
				Grams.	Grams.	Grams.	Grams.
Normal diet. . .	3	6.00	5.10	13.50	0.92	1.92	4.28
Same + HCl. .	3	5.98	5.36	13.65	1.59	2.15	7.92

In the above experiment 85 c.c. of a solution containing 12 per cent. or 10.2 grams of chlorin was added to the food during three days, being an average of 3.4 grams of chlorin per day. This would require 1.6 grams of ammonia to effect its neutralization. On the third day of acid administration the ammonia rose to an output of 2.03 grams. The phosphates increased 12 per cent. and there was a rise in the acidity of the urine. As the result of these protective agencies the carbon dioxid tension in the blood remained unchanged after the administration of hydrochloric acid.

In certain pathologic states, such as diabetes, phosphorus-poisoning, nephritis in some of its forms, the so-called food intoxication of infants,[2] and other conditions, there is an increased production of ammonia in the body for the neutralization of acids of endogenous origin. This may be accompanied by a withdrawal of body alkali, so that the power to combine

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[1] Begun, Herrmann, and Münzer: "Biochemische Zeitschrift," 1915, lxxi, 255.

[2] Howland and Marriott: "American Journal of Diseases of Children," 1916, xi, 309.

with carbon dioxid is greatly reduced and the alveolar tension of CO_2 falls in consequence. However, even under these conditions the reaction of the blood may remain unaffected. This is strikingly illustrated in the experiments of Poulton[1] on cases suffering from severe diabetes, in which condition β-oxybutyric acid is largely formed. (See table, p. 468.)

The blood of the first six patients showed a normal P_H. Only in the depth of coma a few hours before death is there a distinct fall in alkalinity, and, indeed, this fall may not be as great as in a normal person after climbing a thousand feet in twenty-five minutes, under which circumstances the P_H may be 7.09 (see p. 322).

It is evident that the reaction of the blood in severe diabetes is maintained at the normal through the reduction of its carbon dioxid content. Such a reduction in carbon dioxid combining power indicates a reduction in the alkali reserve of the blood, and forms the basis of the important method of Van Slyke for investigating the intensity of acidosis.

That ammonia in the urine is an indicator of acid formation and not due to a pathologic disturbance of urea formation was shown by Muenzer,[2] who gave alkali in cirrhosis of the liver and reduced the quantity of ammonia elimination to normal. Fiske and Karsner[3] find that livers which have been severely damaged in the living animal by administration of chloroform, phosphorus, hemolytic immune sera, hydrazin sulphate, or phlorhizin still preserve the power of transforming perfused ammonium carbonate into urea. Janney,[4] in von Müller's laboratory, gave bicarbonate of sodium to men and found that the quantity of ammonia in the urine was reduced to almost undeterminable traces; hence the ammonia in the urine has as its sole function the neutralization of acid bodies and ceases to be formed in the presence of an excess of fixed alkali.

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[1] Poulton: Proceedings of the Physiological Society, p. i; "Journal of Physiology," 1915, l.

[2] Muenzer: "Deutsches Archiv. für klin. Med.," 1894, lii, 199 and 417.

[3] Fiske and Karsner: "Journal of Biological Chemistry," 1914, xviii, 381.

[4] Janney: "Zeitschrift für physiologische Chemie," 1911–12, lxxvi, 99.

Howland and Marriott[1] find that the administration of acid phosphates causes no increase in ammonia in the urine.

Klein and Moritz[2] found that on the day following a diet which was rich in fat there was an increase in the quantity of fixed alkali in the urine and a corresponding fall in the quantity of ammonia. They interpret the results as signifying that the alkali was temporarily involved in fat metabolism (formation of soaps) and was eliminated when this need was no longer present.

The consideration of the ingestion of alkalies and bases in the food will be discussed in the chapter on A Normal Diet.

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[1] Howland and Marriott: Reported at the meeting of the American Physiological Society, December, 1916.

[2] Klein and Moritz: "Deutsches Archiv für klin. Med.," 1910, xcix, 162.

CHAPTER VII

THE INFLUENCE OF PROTEIN FOOD (Concluded)

PART III—THE RESPIRATORY METABOLISM

The discussion of the more important details of the breakdown of amino-acids in the organism reveals the modern beginning of mental penetration into the biochemical reactions in the organism.

The gross results of protein ingestion are to be ascertained by other means, by a study of the respiratory metabolism and by calorimeter observations.

Bidder and Schmidt[1] gave meat to the full extent of its appetite to a cat which had previously been starved and reported the following figures for the respiratory exchange:

	CO_2 Grams.	O_2 Grams.
Fasting	53.52	50.18
Excessive meat ingestion	113.52	103.84

Many subsequent experiments have brought to light this characteristic increase in metabolism after the ingestion of protein in excess.

In 1862 Pettenkofer and Voit (see p. 155) noted that after giving meat in large quantity a portion of the carbon of the protein metabolized was retained in the body, which they interpreted as indicating a production of fat from protein. Frank and Trommsdorff[2] and also Rubner[3] gave meat in large amount to dogs, and determined the carbonic acid output of the animals during intervals lasting between three to six hours.

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[1] Bidder and Schmidt: "Verdauungssäfte und Stoffwechsel," 1852, p. 356.

[2] Frank and Trommsdorff: "Zeitschrift für Biologie," 1902, xliii, 266.

[3] Rubner: "Gesetze des Energieverbrauchs," 1902, p. 365.

The first named authors noted that although the urinary nitrogen elimination showed a maximum rise of nearly eight times that of fasting and varied greatly, the carbonic acid elimination was not so largely increased and was much more even.

The details of the results following the ingestion of large quantities of meat by a dog are to be found in the calorimetric observations of Williams, Riche, and Lusk.[1] These authors made observations in hourly periods upon the nitrogen in the urine, the carbonic acid elimination and oxygen absorption, and the heat production of a dog following the ingestion of 1200 grams of meat. The results are in part presented in the accompanying curve:

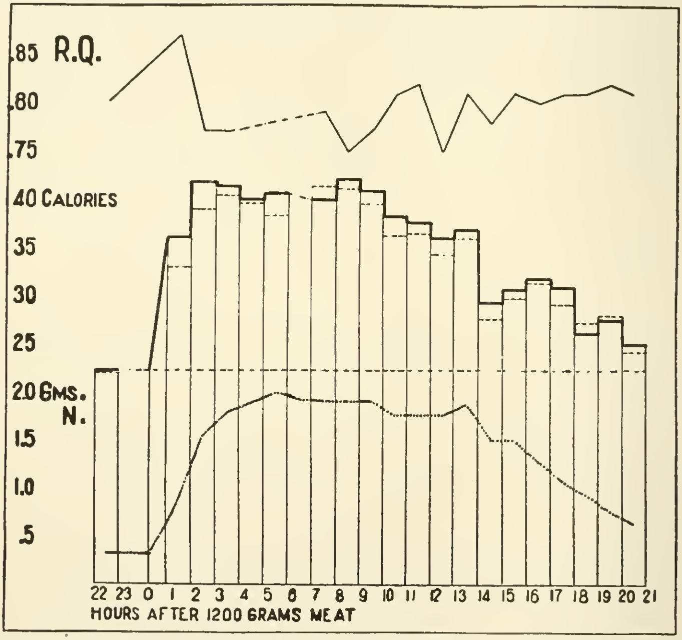

Fig. 15.—Showing the R. Q., the total metabolism determined by indirect (heavy black line) and direct (broken line) calorimetry, as well as the nitrogen elimination (dotted line), during hourly periods after the ingestion of 1200 grams of meat.

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[1] Williams, Riche, and Lusk: "Journal of Biological Chemistry," 1912, xii, 349.

During the fourth hour the nitrogen in the urine reached a level of 1.80 grams and remained between 1.76 and 2 grams per hour during a period of eleven hours. During this period the heat production was nearly twice the normal basal metabolism, and the increase was proportional to the increase in protein metabolized as calculated from the increased nitrogen elimination above that of the basal metabolism. However, during the second and third hours, in which the increase in heat production almost reached its maximum, the urinary nitrogen was only 0.89 and 1.55 grams respectively. This is due to the fact that urea was accumulating in the blood and the quantity of its elimination in the urine did not at first truly represent the intensity of the metabolism of protein (see p. 173). This fact is made certain by the curve of glucose and nitrogen elimination obtained by Janney[1] after giving serum albumin to a phlorhizinized dog (see p. 243). In this curve the glucose elimination reached its maximum during the first hour, the nitrogen elimination during the fifth. It seems also probable that after giving 1200 grams of meat to the normal dog the establishment of a plateau of even nitrogen elimination indicates that during this period the influx of protein nitrogen from the intestine equalled its destruction within the cells and its outgo through the urine. When a fall in the nitrogen output set in, the metabolism also fell as the result of the decrease in protein metabolism.

During an experimental period of twenty-two hours the heat production calculated from the excreta was 738.5 calories, and directly measured by the calorimeter was 718.5 calories, a difference of 20 calories, or 2.7 per cent. During the first two experimental hours there was always a considerable discrepancy between indirect and direct calorimetry. It is now certain that this was due to the fact that the meat was given when cold (see p. 123). Allowing for this error, the indirect and direct methods agree within less than 2 per cent.

An interesting fact revealed in the analysis of the respira-

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[1] Janney: "Journal of Biological Chemistry," 1915, xx, 329.

tory exchange is that, beginning with the second hour and continuing for fourteen hours after the ingestion of protein, the respiratory carbon dioxid is less than that which one would expect if all parts of the protein complex were oxidized. There is, therefore, *carbon retention* during this period. Such carbon might have been retained in the form of carbohydrate or of fat. Schreuer[1] gave 900 and 1500 grams of meat to a dog and determined the metabolism by the Zuntz method from three to four hours after meat ingestion. He concluded from the respiratory quotient that carbon derived from protein was retained in the form of carbohydrate. New confirmation of the conversion of part of the protein molecule into glucose was afforded by the oxygen absorption of the dog of Williams, Riche, and Lusk during various periods following the ingestion of 1200 grams of meat. These facts are here set forth:

TABLE CONTRASTING THE ACTUAL OXYGEN INTAKE WITH THAT REQUIRED BY THEORY IF THE CARBON RETENTION HAD BEEN IN THE FORM OF GLYCOGEN OR OF FAT. 1200 GRAMS MEAT INGESTED AT NOON.

Time.	Calories.		C Retained (Calc. as Glucose).	O_2 Actual.	O_2 (Retained as Glucose).	O_2 (C Retained as Fat).
	Found.	Calculated.				
P. M.						
1.45- 2.45..	38.92	41.70	0.10	13.63	12.99	12.95
2.45- 3.45..	40.40	41.29	1.93	13.29	12.56	11.73
3.45- 6.45..	121.91	124.82	7.86	43.25*	40.61	37.23
6.45- 9.45..	122.11	122.86	7.86	40.35	40.01	36.63
9.45-12.45..	106.70	111.67	7.50	35.47	36.41	33.19
12.45- 1.45..	35.86	36.82	3.42	11.34	12.13	10.66
1.45- 2.45..	27.71	29.32	2.75	9.31	9.65	8.47
2.45- 3.45..	64.24	62.36	3.08	19.56	20.19	18.87
	557.85	570.84	34.50	186.20	184.55	169.73
	Dif. = 2.3 per cent.			Dif. = 0.9 per cent.		Dif.=10%

34.5 grams glucose : 28.3 grams N : : 1.2 : 1

* Small leak in the apparatus during this period determined the day following to amount to about 1 gram O_2 per hour.

The respiratory quotients (see Fig. 15) fall during the hours of carbon retention to below that of protein itself

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[1] Schreuer: "Pflüger's Archiv," 1905, cx, 227.

(which is 0.80), because the unoxidized carbohydrate is retained in the organism as glycogen. If the carbon were retained in the organism as fat, the respiratory quotient would rise. If one considers the period between the hours of 6.45 to 9.45 P. M., one obtains the following picture of what occurs:

METABOLISM OF A DOG DURING A THREE-HOUR PERIOD OF MAXIMAL PROTEIN CARBON RETENTION AFTER 1200 GRAMS MEAT.

	Direct.	Indirect. (C Retained = 3.14 Grams.)	
		If Retained as Glucose.	If Retained as Fat.
Calories	122.11	122.86	113.32
Oxygen, grams	40.35	40.01	36.63
Respiratory quotient	0.77	0.77	0.85

It is obvious from these figures that *the oxygen absorption and the heat production prove the retention of carbon either in the form of glucose or glycogen in the organism.* During the fourteen hours of carbon retention following the ingestion of 1200 grams of meat, the actual oxygen absorption was 186.2 grams against a value of 184.5, calculated on the assumption that carbon was stored as glycogen or a difference of 0.9 per cent. If the carbon had been retained as fat, 169.7 grams of oxygen would have been required, or 10 per cent. less.

During these fourteen hours 34.5 grams of glucose were stored as glycogen in the organism and 28.3 grams of N were eliminated in the urine. This yields a D : N ratio of 1.2 : 1. Since 3.6 is the maximum yield of glucose per gram of N in diabetic urine, it is evident that one-third of the glucose derivable from protein in metabolism was retained in the organism and deposited in the liver and other glycogen reservoirs. This represents 20 per cent. of the total energy contained in the protein metabolized.

The production of glucose from protein is not an emergency process as some writers maintain, but it is a normal function.

A question which has aroused great interest is that concerning the production of fat from protein. Pettenkofer and Voit[1] found that after ingesting considerable quantities of protein, although the nitrogen of the protein was eliminated in the urine, a part of the carbon was retained in the body and not excreted by the usual channels. They estimated that meat protein contained 3.68 grams of carbon to each gram of nitrogen. If less than 3.68 grams of carbon appeared in the total excreta when 1 gram of nitrogen was eliminated, then some protein carbon must have been stored in the body. This carbon might have been retained in two forms—as glycogen or as fat. Claude Bernard had shown that glycogen increases in the liver after the ingestion of protein. The retained carbon as observed by Pettenkofer and Voit was in such large quantity as to preclude the possibility of its retention entirely as glycogen, and therefore they concluded that fat must have been prepared from protein and stored up in the body. This afforded an experimental basis for the theory of a production of fat from protein in fatty degeneration.

Later Rubner,[2] in Voit's laboratory, showed that the relation 3.68 C : 1 N in protein, as used by Pettenkofer and Voit, was inaccurate, and that meat fully extracted with ether contains only 3.28 of carbon to one of nitrogen (see p. 39). The polemical arraignment by Pflüger[3] of Voit's older work was based upon these results of Rubner. Instead of there being a great retention of protein carbon, there was none in some experiments and very little in others. The formation of fat from protein was evidently less easy of demonstration than it had seemed.

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[1] Pettenkofer and Voit: "Annalen der Chemie und Pharm.," 1862, II Supplement, pp. 52 and 361; "Zeitschrift für Biologie," 1871, vii, 433.

[2] Rubner: *Ibid.*, 1885, xxi, 324.

[3] Pflüger: "Pflüger's Archiv," 1892, lii, 239.

The subject was investigated anew by Cremer,[1] who starved a cat for many days, and then gave the animal all the lean meat it would eat, or about 450 grams a day. The cat was kept in a respiration apparatus and the total excreta were collected. The carbon belonging to the meat ingested was calculated at the low ratio of 3.18 to 1 of nitrogen. The average daily metabolism during the eight days of meat ingestion is indicated in the following table:

WEIGHTS IN GRAMS

N in urine and feces,	C in			Meat C calculated from N excreted,	C from meat added to the body,
	Urine,	Feces,	Respiration,		
13.0	7.5	1.4	25.4	41.6	7.3
		34.3			

There was a daily excretion of 13 grams of nitrogen corresponding to the liberation of 41.6 grams (13 × 3.18) of protein carbon. But only 34.3 grams of carbon were actually eliminated from the body, and a difference of 7.3 grams was retained in the body; 17.5 per cent. of the protein carbon therefore was not eliminated. For eight days the whole carbon retention was 58 grams, which corresponds to a glycogen production of 130 grams. The cat, however, contained only 35 grams of glycogen, determined after killing it at the end of the experiment. The balance of the carbon must have been stored as fat.

Cremer[2] notes that a cat fed as above contains 1.47 per cent. of muscle glycogen, which is as much as the maximum (1.37 per cent.) found by E. Voit in geese after the ingestion of starch. One should here recall that Pflüger (see p. 175) found as much as 10 per cent. of glycogen in the liver of a previously fasting dog after it had been fed with codfish. This is as much glycogen as would have been deposited after carbohydrate ingestion.

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[1] Cremer: "Zeitschrift für Biologie," 1899, xxxviii, 309.

[2] Cremer: *Ibid.*, 1899, xxxviii, 313.

Since it is known that sugar in excess may be converted into body fat and that meat may yield 58 per cent. of sugar in metabolism, there is every reason to believe that if protein be ingested in excess the deaminized residues of many of the amino-acids may be converted into glycogen, and then, if this pathway be closed through saturation of the body-cells with glycogen, fat is formed instead (see p. 304).

It is quite possible that the origin of fat from protein is in its nature the same as the origin of fat from carbohydrates.

In the first edition of this work (1906, p. 123) it was computed from the investigations of Cremer with the cat and from those of Rubner with a dog that 40 per cent. of the protein carbon which was capable of conversion into glucose could be retained in the organism either as glucose or as fat. This is to be compared with 33 per cent. of such glucose retention indirectly measured by Williams, Riche, and Lusk.

An interesting contribution to the subject of the possible formation of fat from protein has been made by Weinland,[1] who found in the case of the blow-fly (*calliphora*), which lays its eggs in meat, that both the larvæ and a pulp made by crushing them had the power, in the absence of oxygen, to split peptone into amino-acids, deaminize these with evolution of ammonia, and then with evolution of carbon dioxid to produce higher fatty acids, presumably through synthetic union of fragments of the acids which had been freed of their amino groups. Such a procedure reasonably explains the formation of fat from protein in the sense of the older theories (see p. 171).

The question of a "fatty degeneration" of protein under pathologic conditions is another matter and will be considered in another place. (See Chapter XVI.)

The experiments already described bring to light a very striking change in the metabolism after the ingestion of protein in excess. The total heat production is markedly increased. To what may this be due?

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[1] Weinland: "Zeitschrift für Biologie," 1908, li, 197.

Von Mering and Zuntz[1] believed that such increased metabolism was due to the activity of the intestinal tract after the ingestion of food.

Voit[2] criticised this view, and said that a rise in the carbon dioxid excretion from 366 grams in starvation to 783 grams after ingestion of 2500 grams of meat by a dog (see p. 155) was too great to be due to intestinal activity, and, indeed, corresponded to the rise noted only after the hardest exercise. Furthermore, Voit had shown that after giving a medium quantity of fat, the carbon dioxid excretion and oxygen absorption were almost the same as in hunger, notwithstanding the activity of the filled intestine.[3]

This question has received very painstaking and elaborate investigation at the hands of Rubner, who has published his results in a book entitled "Die Gesetze des Energieverbrauchs bei der Ernährung." This volume is an extension of a work of which a preliminary communication was published by Rubner[4] from Voit's Munich laboratory in 1885.

Rubner shows that bones given to a dog will not increase his metabolism in spite of the intestinal irritation, so the increase after meat ingestion is not due to a nerve reflex of mechanical nature. Further, the metabolism is not raised after the ingestion of meat extract, so the chemical stimulus of flavors which start activity in the glands does not affect total metabolism. Again, the ingestion of water in the quantity contained in meat, while it may cause a rise in nitrogen in the urine followed by a fall—the rise being due to a rapid washing out of nitrogenous decomposition products—does not alter the total metabolism in any way.

Lusk[5] has shown that urea when given in the quantity which would be liberated from considerable amounts of meat,

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[1] von Mering and Zuntz: "Pflüger's Archiv," 1877, xv, 634.

[2] Voit: "Physiologie des Stoffwechsels," 1881, p. 209.

[3] Compare also Benedict, F. G., and Pratt: "Journal of Biological Chemistry," 1913, xv, 1.

[4] Rubner: "Sitzungsberichte d. kgl. bayr. Acad. d. Wissenschaft," 1885, Heft 4.

[5] Lusk: "Journal of Biological Chemistry," 1912, xiii, 27.

and sodium chlorid, the ingestion of which might induce osmotic exchanges in the cells, have no effect upon the heat production.

Benedict and Emmes[1] have demonstrated that cathartics and agar-agar when given to man have no effect upon total heat production in spite of the intestinal activity which they produce.

The absence of true "intestinal work" or "Darmarbeit" in the sense of Zuntz is further shown by the fact that Johansson[2] has given a fasting man 75 grams of glucose without the slightest increase in the output of carbon dioxid. If glucose had been consumed the carbon dioxid excretion would have risen (see p. 289), therefore glucose was retained as glycogen. Since all these processes were without effect on the carbon dioxid output, it follows that the intestinal activities involved did not cause an increase in the total metabolism. Of similar import are the results by the same writer after administering 50 grams of glucose to a diabetic. The sugar was absorbed and eliminated in the urine without affecting the carbon dioxid output.

The increase in metabolism is greater in the case of protein than with any other food-stuff. Rubner calls this action of abundant protein food in raising the metabolism the *specific dynamic* action of protein. Rubner found that when dogs were fed with meat their bodies metabolized in largely increased measure without doing any external work. A more rapid respiration alone betokened the increased oxidation and the effort of the body to rid itself of excess of heat through physical regulation. The temperature of the dogs scarcely changed, so perfect is the regulatory mechanism for the discharge of heat. Thus in one dog the temperature was 38.16° before the meal, 38.74° during the digestion, and 38.17° at the end of digestion.

If a large quantity of protein be ingested day after day,

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[1] Benedict, F. G., and Emmes: "American Journal of Physiology," 1912, xxx, 197.

[2] Johansson: "Skan. Archiv für Physiologie," 1909, xxi, 1.

then the usual specific dynamic action occurs and also a continued "secondary" rise in total day-to-day metabolism, which increases with the continual increase in protein metabolism. When nitrogen equilibrium is established the heat production remains constant at a higher level.

Rubner[1] illustrates this important fact in the following experiment on a dog, the food of which contained 17 grams of nitrogen:

Calories in Meat Ingested.	N to Body.	Carbon to Body.	Total Calories of Metabolism.
0	−1.31	....	310.61
0	−1.52	....	278.00
481.5	3.95	2.97	311.43
481.5	2.80	3.70	333.82
481.5	2.30	1.61	368.41
481.5	2.20	2.53	361.70
481.5	0.92	4.45	375.47
481.5	0.20	4.31	395.77
0	−3.70	....	357.20
0	−2.64	....	310.29

This experiment of Rubner shows that the amount of protein carbon retained in the body for the production of carbohydrate or fat has nothing to do with the intensity of the specific dynamic action. Protein retention is much more readily brought about on a mixed diet containing large quantities of carbohydrates, as will be seen in a subsequent chapter.

Thus far in this book the influence of external temperature upon the course of protein metabolism has not been discussed. Rubner has shown that this is a factor of profound significance. It has already been demonstrated how, through *chemical regulation*, the basal requirement of the body is reflexly increased by increasing cold in the environment. Rubner[2] compared the starving metabolism of a dog at different temperatures with that of the same dog when 100, 200, and 320 grams of meat were ingested. The results are presented as follows in terms of calories produced per kilogram of body weight:

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[1] Rubner: "Die Gesetze des Energieverbrauchs," 1902, p. 246.

[2] Rubner: *Ibid.*, p. 109.

INFLUENCE OF EXTERNAL TEMPERATURE ON METABOLISM AFTER PROTEIN INGESTION

Temperature.	Starvation.	100 Gm. Meat or 24 Cal. per Kg.	200 Gm. Meat or 48 Cal. per Kg.	320 Gm. Meat or 81 Cal. per Kg.
7°	86.4	....	77.7	87.9
15°	63.0	....	....	86.6
20°	55.9	55.9	57.9	76.3
25°	54.2	55.5	64.9	
30°	56.2	55.6	63.4	83.0

One hundred grams of meat did not change the metabolism at 20°, 25°, or 30°; 200 grams of meat had no effect at 20° or at 7°, but at 25° and at 30° there was an increase, although the food contained fewer calories than the requirement. With 320 grams of meat there was a great increase above the starvation requirement, except at 7°, where it is a maintenance diet and the metabolism remains unchanged. In other words, at a temperature of 30° the specific dynamic action of this amount of protein is capable of increasing the heat production above that of starvation by about 53 per cent., while at 7° there is no change whatever. It is also evident that at a high temperature even a small quantity of protein, such as 200 grams of meat, causes a considerable rise of metabolism.

Rubner gives the metabolism in terms of calories per kilogram after the ingestion of 550 grams of meat or 173.8 calories per kilogram of body weight in a dog, as follows:

Temperature.	Starvation.	550 Grams Meat.	Increase.
4.2°	128.1	133.5	4.2 per cent.
14.5°	100.9	110.9	9.9 "
22.1°	70.7	101.0	42.9 "
30.7°	62.0	117.2	89.0 "

In certain cases after food ingestion the carbon dioxid excretion may remain constant at different temperatures of environment. This action is seen in the dog mentioned on this page after he had eaten 320 grams of meat at various room temperatures. The increase in body metabolism due to the stimulus of cold (chemical regulation) is not necessary, since heat in excess of the requirement is already available. All that is needed is the arrangement of avenues of escape for the excess of heat produced from the food ingested (physical regulation). This physical regulation is brought about by the evaporation of water and by a change in the distribution of the blood.

How the increased evaporation of water enters as a refrigerating factor is beautifully shown in the experiment on the dog (p. 234) which fasted and then received 100, 200, and 320 grams of meat at various room temperatures. The distribution of the loss of heat by radiation and conduction and by the evaporation of water was as follows:

DISTRIBUTION OF HEAT LOSS FROM A DOG AFTER MEAT INGESTION

Temperature.	Hunger.		100 Grams Meat.		200 Grams Meat.		320 Grams Meat.	
	Cal. from Radiation and Conduction.	Cal. from Evaporation of Water.	Cal. from Radiation and Conduction.	Cal. from Evaporation of Water.	Cal. from Radiation and Conduction.	Cal. from Evaporation of Water.	Cal. from Radiation and Conduction.	Cal. from Evaporation of Water.
7°...	78.5	7.9	....	....	67.1	10.6	78.5	9.4
15°...	55.3	7.7	....	....	46.7	11.2	76.2	10.4
20°...	45.3	10.6	46.7	9.2	49.5	15.4		
25°...	41.0	13.2						
30°...	33.2	23.0	34.1	21.5	27.8	35.6	34.5	48.5

It is evident from the above that the greater part of the loss of heat at a low temperature was by radiation and conduction, but at a high temperature (30°) the loss by the evaporation of water was largely increased. The extra heat production on account of the specific dynamic action of the protein was lost through the increased evaporation of water. Much meat on a hot day would, therefore, seem contraindicated.

While the chemical regulation protects the body from an abnormal fall in temperature, the physical regulation prevents an abnormal rise in temperature. The organism may be at times under the influence of one means of regulation, at times of the other, and without being conscious of any difference. Cold-blooded animals have inadequate chemical regulation, and their temperature falls with that of their surroundings (see p. 114).

A study of the specific dynamic action of protein in its relation to temperature changes gave Rubner[1] new points of view. He saw (experiment on p. 234) that by chemical regulation the metabolism in a fasting dog was increased from 54 to 86 calories per kilogram, an increment of 32. And he likewise observed that after the ingestion of 320 grams of meat the heat produced at a room temperature of 30° rose from 56 in starvation to 83, a difference of 27 calories. The source of the increase through chemical regulation is known to be chiefly in the muscles. The increase brought about by protein ingestion had been shown by Rubner to be due not to any such thing as intestinal activity (see p. 231), but rather to some specific heat-raising effect of protein metabolism itself. It was apparent that these two sources of increased heat might enter into a reciprocal arrangement, because on cooling the atmosphere in which the dog lived to 7° C. the metabolism, after the ingestion of 320 grams of meat, remained at 87.9 calories in contrast with 83.0 on feeding at 30°. Here the heat due to the specific dynamic action was used in replacement of that induced by chemical regulation. This illustrates Rubner's modified idea of his *compensation theory*, or a reciprocity between heat produced in the muscles by chemical regulation and the extra heat production brought about through the ingestion of food.

Since the extra heat production after food ingestion could be utilized instead of heat from chemical regulation, Rubner perceived that the true increase through specific dynamic action could be measured best at the temperature of 33°, where there was no reflex increase in metabolism through chemical regulation.

It was especially important to make experiments regarding

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[1] Rubner: "Energiegesetze," p. 145.

the action of food-stuffs at a temperature of 33°, for that is the temperature with which man surrounds his skin. By means of clothes and artificial heating man constantly tries to remove himself from the influence of chemical regulation. His daily life is practically under the influence of a tropical climate. His metabolism is unchanged from the normal when he is immersed in a bath at 33°.[1]

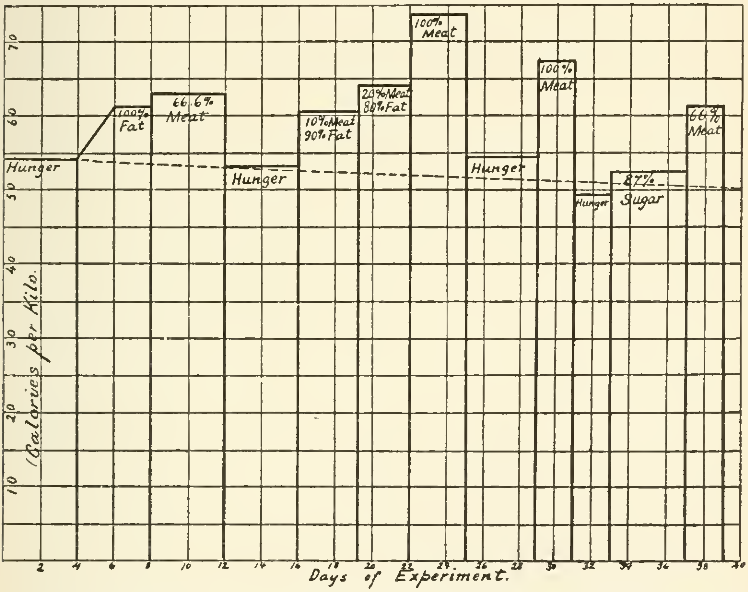

Fig. 16.—Rubner's chart indicating the specific dynamic action of different food-stuffs ingested at a room temperature of 33°. The dotted line indicates the height of the fasting metabolism.

Rubner, therefore, planned an experiment in which a dog was kept at a temperature of 33°. At times the animal was made to fast in order that the basal requirement could be determined, and during other definite periods meat, fat, and carbohydrates, either alone or combined, were ingested, and the increased metabolism due to the varying dietaries was noticed. The experiment extended over a period of forty-six days.

[1] Rubner: "Archiv für Hygiene," 1903, xlvi, 390.

A summary of the results obtained is graphically illustrated by the accompanying Fig. 16, which has been taken from Rubner.[1]

It is clearly evident that meat ingestion raises the metabolism most, fat next, and sugar least of all the food-stuffs. The ingestion of the starvation requirement for energy in the form of fat raises the metabolism 12.7 per cent.; in the form of sugar, 5.8 per cent. During the two periods, when approximately 100 per cent. of the basal requirement was ingested as meat, there was an *average increase* in the metabolism of 36.7 per cent.

After making deductions for the effect of the fat contained in the meat given, Rubner computed that there was an average increase in metabolism of 30.94 calories for 100 calories contained in the protein of the diet in the resting animal when it was outside of the influence of the chemical regulation of temperature. The action of gelatin is similar, the increase in metabolism being 28 per cent. for every 100 calories in the gelatin ingested.

Again Rubner[2] has determined the amount of the metabolism of a fasting dog and that of the same dog made diabetic with phlorhizin (see p. 474). Under the latter circumstances the protein metabolism is greatly increased. He found that for every 100 calories increase in body protein broken down there was an increased heat production of 31.9 calories. Here was a rise in heat production not due to protein ingestion and, therefore, not due to intestinal work, but due to the mere fact of increased protein metabolism in starvation. The specific dynamic action of protein then may thus be tabulated:

INCREASED HEAT PRODUCTION FOR EVERY 100 CALORIES INGESTED OR METABOLIZED

Meat protein	30.9
Gelatin	28.0
Body protein (phlorhizin diabetes)	31.9

The dog of Williams, Riche, and Lusk showed an increase of 30 calories in heat production for every 100

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[1] Rubner: "Energiegesetze," p. 322.

[2] Rubner: *Ibid.*, p. 370.

calories contained in the protein of the 1200 grams of meat ingested.

It has furthermore been shown by Falta, Grote, and Staehelin[1] that casein and the amino-acids resulting from the hydrolysis of casein when given to a dog exert the same specific dynamic action as do the proteins of meat.

That these results are not limited in their application is shown by Rubner's[2] experiment on a man who was given 120 per cent. of the starvation requirement of energy first in the form of sugar and then of meat. The metabolism was as follows:

Starvation	2042	calories	in	24 hours.
Sugar alone	2087	"	"	"
Meat alone	2566	"	"	"

As neither man nor dog ever lives on meat alone except under forced feeding, the results are not usually so pronounced as in the above case.

Average mixed diets, according to Rubner, must contain between 11 and 14 per cent. more than the calories produced in fasting in order to constitute an ingestion minimum for the maintenance of a man in caloric equilibrium.

One must now pass to the discussion of the cause of the specific dynamic action of protein.

In 1881 Voit laid down the principle that the intensity of metabolism in the cells was modified by the quality and quantity of the food materials brought to them by the blood. He believed that the inherent power of the cells to metabolize was augmented by the presence of increased quantities of food-stuffs. Rubner developed another conception. He declared that the fundamental metabolism of a normal warm-blooded animal was always constant, and that the effect of food ingestion did not change this. The increased heat production which followed the taking of food was due to heat developed from a lot of intermediary reactions and oxidations,

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[1] Falta, Grote, and Staehelin: "Hofmeister's Beiträge," 1907, ix, 334.

[2] Rubner: "Energiegesetze," p. 410.

and had nothing whatever to do with the fundamental level of the cellular requirement of energy which was entirely unchanged. Thus, when protein was metabolized it could supply energy for the maintenance of true cellular activity in so far as glucose was produced from it, whereas other intermediary cleavage products were simply oxidized with the production of extra heat, which was in no way involved in the life processes of the cells. The utilization of energy in protein might be compared with the burning of a tree as fuel for the steam engine, the trunk of the tree being used as fuel within the engine for the production of power, whereas the limbs and twigs are burned as brush outside and supply only heat.

The theory may be schematically indicated as follows:

STARVATION REQUIREMENT OF POTENTIAL ENERGY BY CELLS
= 100 CALORIES

140 Calories in Protein of Meat Ingested

40 Calories = free heat liberated in early cleavage, available in replacement of heat of chemical regulation.	100 Calories = Potential energy from protein available for cell life.

This conception was founded on the erroneous idea that sugar exerted little or no specific dynamic action (see p. 294).

Experiments were instituted in the author's laboratory[1] with the intention of more fully establishing the truth of Rubner's theories of specific dynamic action.[2] It was known that glycocoll and alanin were completely convertible into glucose in the diabetic organism, whereas glutamic acid was in part so converted, three of its five carbon atoms passing into glucose, the other two being oxidized. It follows from Rubner's hypothesis that glycocoll and alanin should exert no specific dynamic action, whereas glutamic acid should manifest this phenomenon. The reverse proved to be true: glycocoll and alanin are capable of greatly increasing the heat production, whereas the strong dibasic glutamic acid is without influence. Glycocoll and alanin produce powerful

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[1] Lusk: "Journal of Biological Chemistry," 1912–13, xiii, 155.

[2] The argument here presented is to be found in Lusk: "Journal of Biological Chemistry," 1915, xx, p. viii.

effects, lasting eight and five hours respectively, whereas on giving those quantities of glucose into which the amino-acids are convertible only an almost negligible influence is observable.

These facts are brought out in Fig. 17. It should be remembered that 25 grams of glycocoll and 20 grams of alanin are each convertible into 20 grams of glucose. Leucin and tyrosin exerted only a slight effect upon the heat production. A mixture of 5.5 grams each of glycocoll, alanin, glutamic acid, and tyrosin, containing 3.46 grams of nitrogen, produced about the same specific dynamic action as 100 grams of meat which contain about 3 grams of nitrogen.

The curve of nitrogen elimination shown in Fig. 17 does not truly represent the rapidity of the metabolism of the amino-acids. If instead of using the hourly extra nitrogen elimination after giving

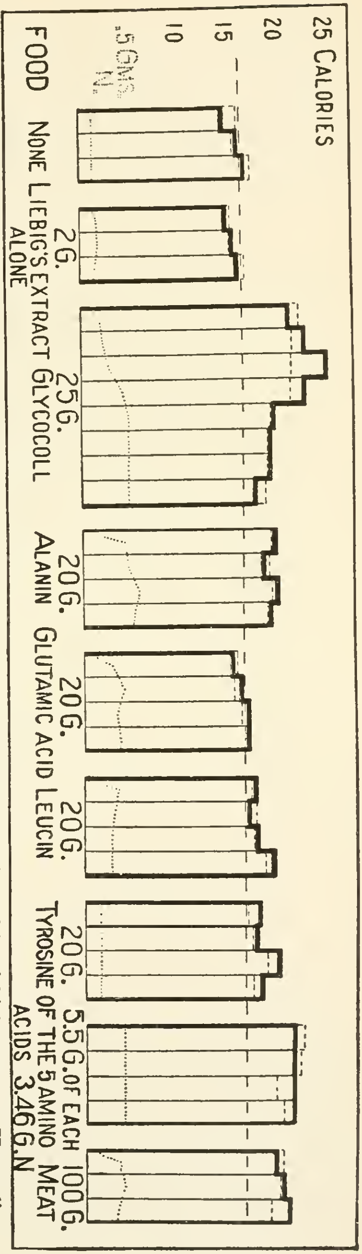

Fig. 17.—Dog II. Hourly metabolism beginning the second hour after giving amino-acids with Liebig's extract. Heavy line—calories calculated. Broken line—calories found. Dotted line—nitrogen of protein plus amino-acid eliminated.

glycocoll or alanin one employs the "extra glucose" elimination after giving these substances to a dog with phlorhizin glycosuria, it is discovered that the maximum breakdown of the amino-acid takes place during the second hour after their ingestion. The following chart (Fig. 18) shows such experiments as accomplished by Csonka:[1]

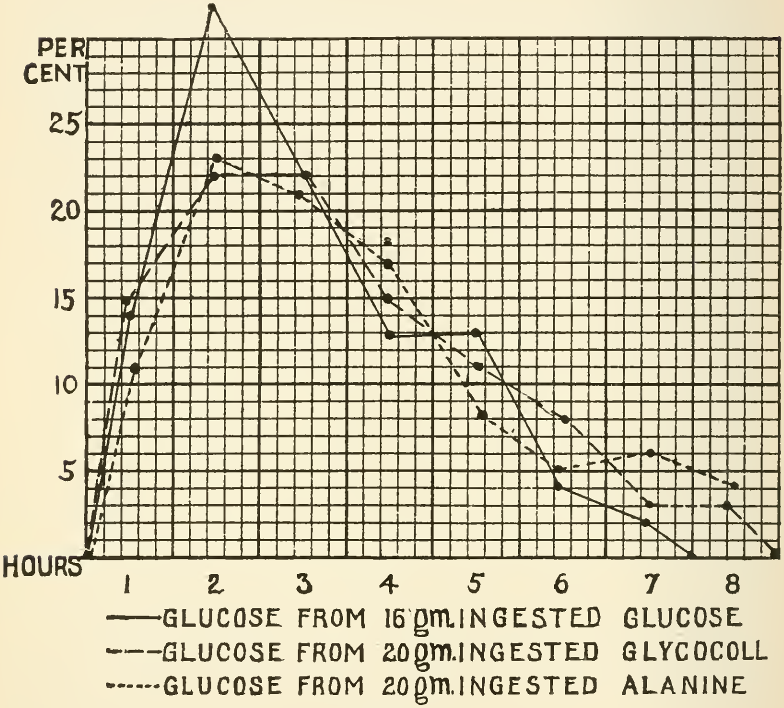

Fig. 18.

This chart shows that the rapidity of the absorption and elimination of glucose ingested in phlorhizin glycosuria is almost the same as the rapidity of the absorption, deamination, synthetic sugar production, and the elimination of such sugar after the administration of an iso-glucogenic quantity of glycocoll and a comparable quantity of alanin.

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[1] Csonka: "Journal of Biological Chemistry," 1915, xx, 539.

It may be added that Janney[1] reports that after giving meat to a phlorhizinized dog the extra sugar appears in the urine quite as rapidly as after giving glycocoll or alanin. The rapidity of the attack of digestive enzymes upon protein must, therefore, be much greater than has hitherto been supposed.

Using the results obtained with glycocoll and alanin, Lusk[2] found that the hours of the greatest heat production after the administration of these substances were coincident with the hours of their greatest metabolism. Also, it was found that the increase in metabolism after giving glycocoll and alanin together is equal to the sum of the effects produced by either alone. Furthermore, the increase of metabolism after giving 20 grams of glycocoll is twice as great as after giving 10 grams. Similar relations obtain after different quantities of alanin. This accords with Rubner's discovery that the intensity of the specific dynamic action is proportional to the quantity of protein ingested. When one compares the heat-increasing power of glycocoll and alanin upon metabolism, it is found that this power is not proportional to their respective abilities to form sugar, but rather to the number of molecules of glycollic and lactic acids which they are respectively supposed to yield on deamination.

It was found in one experiment that the entire energy content of the ingested glycocoll reappeared in the extra output of energy given off by the dog in the form of heat. The course of inquiry into this phenomenon which naturally suggests itself is whether glycocoll is without action upon the body-cells; that is, whether it merely explodes and yields heat, or whether it directly stimulates the cells, thereby raising metabolism to a higher level. This point was determined by giving glycocoll to a phlorhizinized animal. Under these circumstances there is no oxidation of the material ingested and the energy content of the glycocoll is eliminated in the

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[1] Janney: "Journal of Biological Chemistry," 1915, xxii, 191.

[2] Lusk: *Ibid.*, 1915, xx, 555.

urine in the form of sugar and urea. The metabolism was largely increased, notwithstanding the fact that there was no oxidation of the ingested material. Exactly the same phenomenon followed the ingestion of alanin in phlorhizin glycosuria. The ingestion of glucose was without effect even after 70 grams had been given. The cause of the specific dynamic action of glycocoll and alanin therefore lies in a chemical stimulation of the cells, causing them to metabolize more material. This confirms the older view of Voit that the action of food increases the power of the cells to metabolize.

An experiment[1] which shows the effect of giving 20 grams of glycocoll to a phlorhizinized dog is here reproduced:

DOG III, MARCH 25, 1915, EXPERIMENT 104. BASAL PHLORHIZIN METABOLISM AS AFFECTED BY 20 GRAMS OF GLYCOCOLL IN 210 C.C. OF WATER AT 38° PLUS 1 GRAM OF LIEBIG'S EXTRACT

Hours.		R. Q.	Calories.	
			Indirect.	Direct.
1	Basal............	0.733	23.78	24.53
2	"	0.716	23.82	23.84
	Average........	0.724	23.80	24.18
3	Glycocoll, 20 grams			
4		0.707	34.21	32.34
5		0.745	31.65	29.47
6		0.700	29.24	30.07
7		0.702	25.99	26.85
	Average........	0.720	30.27	29.68

Although glycocoll was not oxidized, but appeared as glucose and urea in the urine, yet there was a considerable increase in the heat production after its ingestion in phlorhizin glycosuria. It is, therefore, evident that the cause of the specific dynamic action of glycocoll is independent of the oxidation of glycocoll or the liberation of its energy content. These results, which were first presented at the International

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[1] Lusk: *Loc. cit.*, p. 612.

Physiological Congress held in Groningen in 1913,[1] have been fully confirmed by Grafe,[2] who reports that after giving 50 grams of glycocoll to a normal dog the oxygen absorption rose 77 per cent., while in man the increase was 14 per cent.

The chemical stimulus to the cells does not reside in the amino-acids themselves, for there is no accumulation of amino-acids in the tissues after the ingestion of meat in large quantities. (See Van Slyke, Wishart, p. 80.) Also when protein is deposited in the form of new tissues these amino-acids exert no specific dynamic influence. Rubner[3] gives the following example of the stage of the deposit of protein without a rise in the metabolism of a dog:

	N TO BODY.	CALORIES PER KG.
Starvation	.....	43.26
Meat	+8.7	44.48

The researches of Hoobler[4] have shown the same to be true of the baby, as appears from the following data:

	PROTEIN INGESTED.	PROTEIN DESTROYED.	PROTEIN ADDED TO BODY.	CALORIES OF METABOLISM.
	Grams.	Grams.	Grams.	
High protein diet...	33.1	18.0	15.1	363
High protein diet...	43.3	18.9	24.4	363

Such facts demonstrate that the mere absorption of amino-acids and their rebuilding into new protoplasm does not increase the metabolism.

Since the hours of the highest heat production after giving glycocoll and alanin are the hours of the maximal metabolism of these amino-acids, it is obvious that the metabolism products, such as glycollic or lactic acids (see pp. 190–194), are indicated as the probable chemical stimuli which act upon the

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[1] Lusk: "Archives of Internal Medicine," 1913, xii, 485.

[2] Grafe: "Deutsches Archiv für klin. Med.," 1915, cxviii, 1.

[3] Rubner: "Gesetze des Energieverbrauchs," 1902, p. 256.

[4] Hoobler: "American Journal of Diseases of Children," 1915, x, 153.

protoplasm of the cells, causing them to oxidize materials in increased measure.

One recalls in this connection the permanently increased metabolism in phosphorus-poisoning, in severe anemias, and in persons living at high altitudes, under all of which conditions lactic acid is found in increased amounts in the blood and often in the urine. (See Chapter XV.)

That the chemical stimulus acts on protoplasm directly and not through excitation of the nervous system is to be inferred from the experiments of Tangl,[1] who noticed an increase in the heat production of curarized dogs after giving them protein.

External cold acts reflexly through the nervous system to increase metabolism in a fasting animal and thus prevents a fall in body temperature through the "chemical regulation" of body temperature. According to Rubner's hypothesis, the "free heat" liberated in the intermediary metabolism of protein can be used in lieu of that derived from the increased metabolism induced through the effect of cold. In the light of the newer researches, however, the extra heat necessary to preserve the body from a fall in temperature may be derived from an increased metabolism of the cell itself, whether this be induced by nerve action or by direct chemical stimulation.

It may be that the mass action of the various fragments produced in the breakdown of protein in metabolism is also a contributory factor in the higher production of heat, but that it is the main factor is negatived by contrasting the different effect of 20 grams of glutamic acid with that of 20 grams of glycocoll, the effect of the first being *nil* and that of the latter powerful.

The influence of meat ingestion in man is given in the following table:

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[1] Tangl: "Biochemische Zeitschrift," 1911, xxxiv, 1.

TABLE SHOWING THE PERCENTAGE INCREASE IN METABOLISM EACH HOUR AFTER THE INGESTION OF MEAT BY MAN

AUTHOR.	N IN MEAT.	INCREASE IN METABOLISM IN PER CENT.									
		1	2	3	4	5	6	7	8	10	11
	Grams.										
Magnus-Levy[1]	12	8	6	22	32	24	34	26			
Gephart and Du Bois[2]	10.5	..	..	8	16	12	15	7			
Gephart and Du Bois[2]	23.9*	..	..	..	15	16	28	27	18	26	

* Chopped meat 725 grams + 100 grams fat.

In the last-named experiment protein furnished between 25 and 40 per cent. of the total calories of metabolism instead of the average normal of 15 per cent. When Grafe[3] administered 80 grams of alanin or 50 grams of glycocoll to a man the specific dynamic action caused an increase in the oxygen absorption of 7 and 14 per cent. respectively. The specific dynamic action of protein is not usually as great in man as in the dog. Du Bois[4], however, has seen a rise of 55 per cent. in the metabolism of an achondroplastic dwarf after giving him 750 grams of meat.

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[1] Magnus-Levy: "Pflüger's Archiv," 1894, lv, 87.

[2] Gephart and Du Bois: "Archives of Internal Medicine," 1915, xv, 835.

[3] Grafe: *Loc. cit.*

[4] Unpublished.

CHAPTER VIII

THE INFLUENCE OF THE INGESTION OF FAT

In a previous chapter it was shown that the amount of fat in the fasting organism materially affected the amount of protein burned. Where there was much fat present little protein was consumed; where there was little fat, much protein burned; and where there was no fat, protein alone yielded the energy necessary for life.

The ingestion of fat alone will not prevent the death of the organism because there is a continual loss of tissue protein from the body, which finally weakens some vital organ to such an extent that death takes place.

In a fasting animal which still contained fat, Voit[1] found that the ingestion of 100, 200, and 300 grams of fat scarcely influenced the protein metabolism. The latter was slightly increased, if anything. Voit's table is as follows:

Fat.	Urea.	Fat.	Urea.
0	11.9	300	12.0
0	12.0	0	11.9
100	12.0	0	11.3
200	12.4		

These results have been confirmed by Bartmann,[2] who noted that fat given to the extent of 150 per cent. of the energy requirement was readily absorbed and spared protein to a maximum of 7 per cent. Sometimes when much fat was given there was an increased elimination of nitrogen in the urine, at which time there was also an increased amount of nitrogen in the stools.

[1] Voit: "Physiologie des Stoffwechsels und der Ernährung," 1881, p. 128.
[2] Bartmann: "Zeitschrift für Biologie," 1912, lviii, 375.

To another dog, which in starvation burned 96 grams of fat, Voit gave 100 grams, with the result that it then burned 97 grams. The conditions of the metabolism in these cases were therefore identical. The fat ingested simply burned instead of the body's fat, but the total amount of protein and fat burned remained the same.

One reason why the ingestion of fat up to the requirement does not alter the metabolism may be found in the observation of Schulz[1] that in starvation there is an increase in the quantity of fat in the blood, and of Rosenfeld[2] that the amount of fat in the liver increases. He finds that a fasting liver contains 10 per cent. of fat. If carbohydrates or protein (which yields carbohydrate in metabolism) be ingested, the fat content falls to 6.2 per cent. If fat be given to a fasting dog, the liver may contain 25 per cent. of fat; but if carbohydrates are ingested at the same time, the liver does not retain the fat, which must be deposited elsewhere. Thus, in the liver there is an antagonism between glycogen deposit, which follows carbohydrate ingestion, and fat deposition.

Pflüger[3] gave a dog fat alone in large quantities for thirty days and found that the fresh substance of the liver at the end of the period contained 45 per cent. of fat and no glycogen.

Miescher found fat globules in the muscle-cells of salmon after their five to fifteen months' fast in fresh water, during which time they had laid their eggs. It is undoubted that the deposits of fat in the adipose tissue of these fishes are drawn on in starvation, and that the blood then carries to the hungry cells all the fat they require for their continued function. Greene[4] states that large quantities of fat are present in the fibers of the great lateral muscle of the Columbia River salmon at the beginning of its travels up the river, and this fat remains there in strikingly uniform quantity during the whole of the migration journey. It seems that the fat supply to the cells

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[1] Schulz: "Pflüger's Archiv," 1896, lxv, 299.
[2] Rosenfeld: "Ergebnisse der Physiologie," 1903, ii, I, 86.
[3] Pflüger: "Pflüger's Archiv," 1907, cxix, 123.
[4] Greene: "Journal of Biological Chemistry," 1912, xi, p. xviii.

is regulated by the quantity of other foods available, and that even in starvation there is at first ample fat to meet the requirement of the organism (see p. 100). These are important principles which will be further discussed when the subject of fatty infiltration is considered. (See chapter on Diabetes.)

The method of the oxidation of fat has already been described (see p. 182), and one would expect to find β-oxybutyric acid as an end-product of this metabolism. In fact, the blood of normal human subjects, as well as the blood of dogs, pigs, and cattle, contains usually a little less than 1.5 mg. of β-oxybutyric acid in 100 c.c.[1] Sassa[2] reports between 1 and 2 mg. to be widely distributed in the blood and organs of man and various mammals. In normal conditions this end-product is, therefore, present in only minimal amounts.

When fat is oxidized in excess, as in fasting, β-oxybutyric acid appears in the urine (see p. 182). So also when fat forms the main portion of the diet the same phenomenon occurs. Forssner[3] gave a man a diet which contained 3380 calories, of which only 160 were in carbohydrate. The last meal was taken at 4.00 P. M., and then olive oil was given at 9.00 P. M. The urines between 11.00 P. M. and 10.00 A. M. contained the following amounts of acetone bodies:

	Total Acetone Bodies, Grams.	β-Oxybutyric Acid, Grams.
No olive oil	5.11	3.69
40 grams olive oil	9.16	7.22
60 grams olive oil	9.96	8.08
80 grams olive oil	11.80	9.52

These results indicate the formation of β-oxybutyric acid in large amounts.

The work of Bloor[4] has shown that after giving fat to a dog there is a gradual rise in the fat content of the blood, the

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[1] Marriott: "Journal of Biological Chemistry," 1914, xviii, 507.

[2] Sassa: "Biochemische Zeitschrift," 1914, lix, 362.

[3] Forssner: "Skan. Archiv für Physiologie," 1910, xxiii, 305.

[4] Bloor: "Journal of Biological Chemistry," 1914, xix, 1.

maximum being attained in the sixth hour, after which there is a fall. The following shows an example:

	BLOOD-FAT PER CENT.
24 hours after food	0.6
3¼ hours after 100 c.c. olive oil	0.73
6¼ hours after 100 c.c. olive oil	1.20
8 hours after 100 c.c. olive oil	0.87

Furthermore, when fat was injected intravenously in such quantity that the fat content of the blood was doubled, the excess disappeared within five minutes after the cessation of the injection.

Work of fundamental character by Magnus-Levy[1] showed the influence of the ingestion of very fat bacon upon the metabolism of the dog. Respiration experiments lasting about thirty minutes each, using the Zuntz method, were made upon a dog breathing through a tracheal cannula. These showed that after giving 140 grams of fat bacon the metabolism increased from the end of the third hour through the eighth to a height which was about 10 per cent. above the original basal level as measured twenty-four hours after the last ingestion of food. After 320 grams of fat bacon had been taken the metabolism showed a maximal increase of 19 per cent. from the end of the third hour through the sixth. The increased metabolism extended from the fourth to the thirteenth hours after food ingestion, and then subsided to the original basal level. The total increase in heat production could be estimated as 2.5 per cent. of the energy content of the fat ingested. The environmental temperature of the dog varied between 16° and 19°, and all extraneous movements were avoided.

In man, after the administration of 210 grams of butter, Magnus-Levy noted a maximal increase of 9 to 14 per cent. above the basal metabolism during the seventh hour. During the eighth hour the increase was only 6 to 8 per cent. above the basal metabolism.

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[1] Magnus-Levy, A.: "Arch. f. d. ges. Physiol.," 1894, lv, 1.

The influence of external temperature on the heat production after ingesting fat above the requirement is similar to that after meat ingestion, only not so pronounced. Rubner[1] gives the following table, showing the effect of the ingestion of 171.3 calories in fat per kilogram of dog:

SPECIFIC DYNAMIC ACTION OF FAT

171.3 calories in fat per kg. dog were ingested.

	Calories per Kilo.		
Temperature.	Starvation.	After Fat Ingestion.	Increase.
2.7°	152.1	155.5	+ 2.2 per cent.
15.5°	83.1	93.4	+12.4 "
31.0°	64.5	79.9	+23.9 "

At 2.7° the excess ingested above the requirement amounted to 12.6 per cent., and the increase in heat production was 2.2 per cent. At 31° the excess of food calories above the requirement was 165 per cent., and the increase in heat production was 23.9 per cent. In this instance 100 per cent. of the requirement may be calculated to raise the metabolism 14.4 per cent. at a temperature of 31°. This represents the specific dynamic effect of fat on the metabolism.

Murlin and Lusk[2] were not able to find so great a specific dynamic action in the dog as Rubner found. They gave to a dog an emulsion containing 75 grams of fat with 692 calories of energy, or 145 per cent. of the basal energy requirement of the animal. The total increase of heat production was 28.8 calories or 4.1 per cent. of the energy in the fat. The experiments were carried out at an environmental temperature of 26° to 27° in a respiration calorimeter, and the results are plotted in the form of a chart, as shown on p. 253. (For the effect of glucose and fat see also p. 300.)

The experiment shows that after the ingestion of fat the heat production gradually rises till the sixth hour to a maximum 30 per cent. above the basal metabolism, and then falls slowly to the basal level, which is reached ten hours after the

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[1] Rubner: "Energiegesetze," 1902, p. 119.

[2] Murlin and Lusk: "Journal of Biological Chemistry," 1915, xxii, 15.

fat has been taken (Fig. 19). This curve of increasing metabolism accords with the curve of increasing fat content in

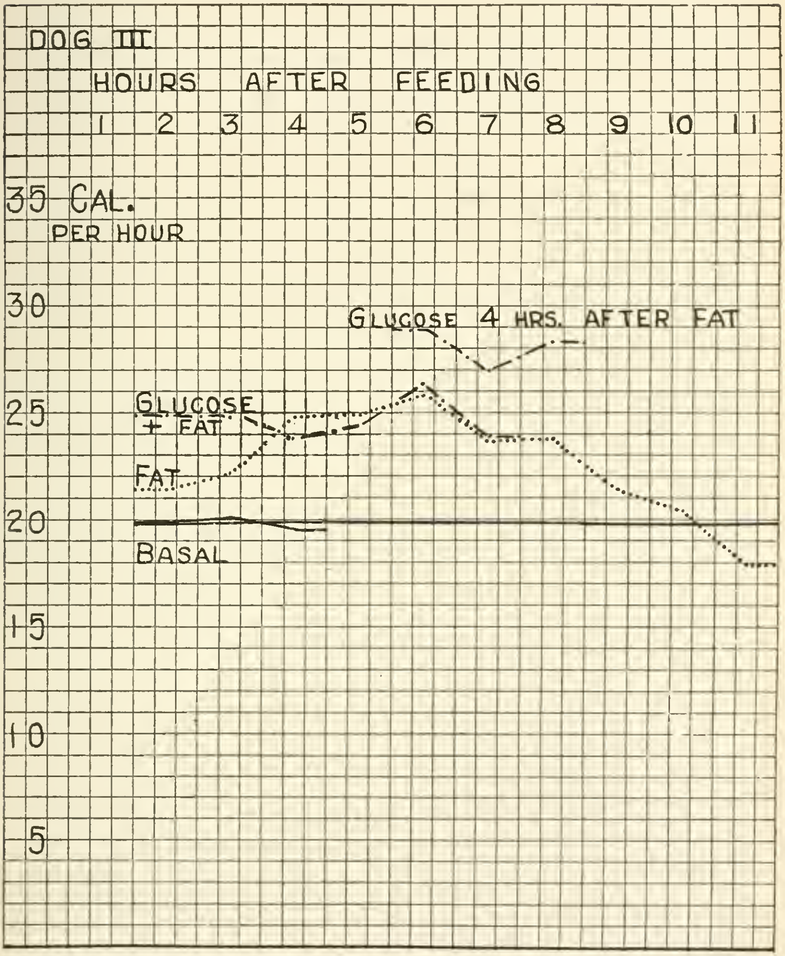

Fig. 19.—The effect of fat and of glucose plus fat upon the heat production.

the blood as shown by Bloor, and indicates that the heat production may be increased by increasing the number of metabolites available for cell nutrition.

It appears from the respiratory quotients that the increase in heat production is entirely at the expense of ingested fat. The respiratory quotients as determined for the basal metabolism averaged 0.84, and after fat ingestion 0.79. Calculation showed that the amounts of protein and glycogen oxidized during the two series of experiments were identical, so that *the extra heat production after giving fat was derived from fat itself.*

It has already been demonstrated that less protein is burned in starvation when the body is fat than when it is lean. It would, therefore, seem that if protein and fat were ingested together, a similar reduction in the amount of the protein requirement would be effected (Voit).

It has been shown in a previous chapter that nitrogenous equilibrium can be maintained in a dog only after the ingestion of three and a half times the quantity of protein destroyed in starvation (see p. 154).

E. Voit and Korkunoff,[1] continuing these experiments, find that if fat and meat be ingested together, the quantity of the latter necessary to establish nitrogenous equilibrium is reduced to between 1.6 to 2.1 times the starvation minimum. Much less protein food is, therefore, required to maintain the body's protein when it is ingested with fat than when it is given alone.

Thus Thomas[2] could not maintain nitrogen equilibrium when twice the amount of the fasting nitrogen elimination was given to a man in the form of meat alone, but was able to accomplish this when meat to the extent of that destroyed in fasting was administered with fat. In consequence of this, protein is more readily added to the body when fat is ingested with it, as is seen in the following experiment of Rubner[3] on a man:

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[1] Voit and Korkunoff: "Zeitschrift für Biologie," 1895, xxxii, 117.
[2] Thomas: "Archiv für Physiologie," 1910, Supplement, p. 249.
[3] Rubner: von Leyden's "Handbuch der Ernährungstherapie," 1903, i, 43.

INFLUENCE OF FAT INGESTION ON NITROGEN RETENTION

Food.			N Metabolism.	
N.	Fat.	Carbohydrates.	N in Excreta.	N to Body.
23.6	99.	260	26.36	−3.64
23.5	195.	226	21.55	+1.85
23.0	214.	221	18.5	+4.13
23.4	350.	234	17.6	+5.75

With increasing quantities of fat there is an increasing addition of protein to the body.

It has already been shown that protein ingested alone in large quantity establishes nitrogen equilibrium at a higher level, constantly raising the amount of heat produced until nitrogenous equilibrium is reached (the secondary dynamic rise, p. 233).

The same destruction of the easily oxidized protein takes place when it is given with fat, as was shown by Voit[1] in the following experiment on a dog:

THE "SECONDARY RISE" IN PROTEIN METABOLISM ON A MEAT-FAT DIET

(Weights in Grams.)

Food.			
Meat.	Fat.	Urea.	Flesh to Body.
1800	0	127.9	26
1800	0	127.6	26
1800	250	117.9	162
1800	250	113.5	171
1800	250	120.7	
1800	250	115.7	164
1800	250	119.7	
1800	250	127.5	11
1800	250	130.0	

A prolonged deposition of protein in the normal adult, when fat is given with it, is demonstrably difficult.

The question arises, Does the ingestion of large quantities of fat also cause an increase in the metabolism until fat combustion is balanced by its ingestion?

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[1] Voit: Hermann's Handbuch, "Physiologie des Stoffwechsels," 1881, p. 131.

Rubner[1] has shown that this is not the case. He cites the record of the following long respiration experiment on a dog which was given 80 grams of meat and 30 grams of fat daily:

ABSENCE OF THE "SECONDARY DYNAMIC RISE" IN FAT METABOLISM ON A MEAT-FAT DIET

(Fat being given in excess of the requirement.)

CALORIES OF METABOLISM.

PROTEIN.	FAT.	TOTAL.
97.2	173.0	270.0
83.0	178.0	261.1
89.3	173.5	262.7
85.6	163.2	248.9
87.8	169.0	256.8
83.0	159.6	242.6
74.4	171.7	246.2
78.0	178.4	256.3
80.0	179.6	259.7

The diet was 58.7 per cent. above the starvation requirement. It contained 354 calories, of which 21.5 per cent. were in protein. The mean heat production during the period of ingestion of food was 256.0 calories, and in the following starvation days 223.2 calories, showing an increase in metabolism of 11.2 per cent. caused by an excess in food of 58.7 per cent. During the later days the animal was in nitrogenous equilibrium. Notwithstanding an excess of fat in the diet, and a continued deposit of fat in the body, there was no increase in the metabolism during the time of experimentation. The secondary dynamic action noted by Rubner as regards protein does not, therefore, take place as regards fat. The storage of fat in the body is consequently a matter of comparative ease.

Rubner[2] has compared the metabolism of a boy who was obese with that of his brother, who was a year older, but thin. They were the children of parents of small means and would not naturally be overfed. The interesting point of the experiment was whether obesity was due to a reduced metabolism with the consequent deposition of fat. Each boy was given a maintenance diet, or one which balanced his metabolism,

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[1] Rubner: "Energiegesetze," 1902, p. 251.

[2] Rubner: "Beiträge zur Ernährung im Knabenalter," 1902.

without adding to or subtracting from his body substance. The general results are as follows:

	Fat Boy.	Thin Boy.
Age in years	10	11
Weight in kilograms	41	26
Total calories of metabolism	1786.1	1352.1
Calories per kilogram	43.6	52.0
Calories per sq. m. surface	1321.	1290.

The comparison shows that the fat brother had a larger total metabolism than the thin one, but the fat boy also had the larger surface. Per square meter of surface the metabolism was the same (see p. 129). The gradual increase in the area of the body caused by filling out the fat cells may therefore increase combustion, but this is not due to the specific action of the fat on metabolism as in the case of the secondary dynamic rise after protein ingestion, but rather to the increase in the size of the body. Carbohydrates, which in excess are converted into fat, must behave in the same way.

It will be noticed that in the experiment where 80 grams of meat and 30 grams of fat were daily ingested, although the protein metabolism gradually fell, the fat metabolism gradually rose, and in isodynamic relation to the fall in protein. Allowing for the difference in specific dynamic action, protein and fat replace each other in metabolism in isodynamic quantities.

CHAPTER IX

THE INFLUENCE OF THE INGESTION OF CARBOHYDRATE

PART I—THE INTERMEDIARY METABOLISM

The preceding chapters have dealt entirely with the subject of the metabolism of protein and fat. The metabolism of carbohydrate has been touched upon incidentally in describing the intermediary metabolism of protein, but the fuller details remain to be considered. Generally speaking, two-thirds of the energy produced by the human organism is derived from the oxidation of carbohydrate. Not without warrant is bread considered the staff of life.

Glycogen.—The gastro-intestinal tract converts starches into glucose, inverts sucrose into glucose and fructose, and lactose into glucose and galactose, so that these soluble monosaccharids become the fuels transported by the blood for the nourishment of the body-cells. The enzymes maltase, invertin, and lactase which, respectively, convert maltose, suchrose, and lactose into monosaccharids, are present in the intestinal mucosa of the newborn infant.[1]

The writer personally prepared fructose from inulin in 1889, which when given to a fasting rabbit caused the formation in its liver of large quantities of glycogen, the anhydrid of glucose.[2] To a lesser extent the same fate may befall ingested galactose. After giving glucose or fructose, as much as 40 per cent. of the dry solids of the liver consisted of glycogen. These monosaccharids were not changed in the intestine.

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[1] Ibrahim: "Zeitschrift für physiologische Chemie," 1910, lxvi, 19.

[2] Voit: "Zeitschrift für Biologie," 1891, xxviii, 245.

Isaac[1] perfused a fluid made up of washed dog's blood-cells and Ringer's solution containing fructose through the liver of a fasting dog and found that the fructose was converted into glucose. The change in the composition of the perfusing fluid was as seen below:

	Before Perfusion.	Three Hours Later.
d-Glucose	0.012 per cent.	0.310 per cent.
d-Fructose	0.349 "	0.020 "

Ishimori[2] has reported that glycogen deposition in the liver follows the intravenous injection of glucose and fructose in the rabbit, although galactose does not have this effect. Galactose is less readily oxidized, at least in the adult organism, than are the other two hexoses (see p. 294), though it may be that the conditions for its breakdown are more favorable in the suckling.

The quantity of glycogen present in a living animal cannot be accurately estimated. Schöndorff[3] gave seven dogs diets rich in carbohydrate for several days, and found that the quantity of glycogen present in their bodies varied between 7.59 and 37.87 grams per kilogram.

The distribution of this glycogen in 100 grams of the fresh tissue varied as follows:

	Maximum.	Minimum.
Liver	18.69	7.3
Muscle	3.72	0.72
Heart	1.32	0.104
Bone	1.90	0.197
Intestines	1.84	0.026
Skin	1.68	0.09
Brain	0.29	0.047
Blood	0.0066	0.0016

The traditional distribution of glycogen, one-half to the liver and one-half to the rest of the body, Schöndorff shows to be incorrect. For 100 grams of liver glycogen there occurred in the rest of the body the following amounts:

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[1] Isaac: "Zeitschrift für physiologische Chemie," 1914, lxxxix, 78.
[2] Ishimori: "Biochemische Zeitschrift," 1912–13, xlviii, 332.
[3] Schöndorff: "Pflüger's Archiv," 1903, xcix, 191.

Dog I	398 grams.
" II	279 "
" III	87 "
" IV	76 "
" V	159 "
" VI	355 "
" VII	105 "

It is an interesting observation of Külz[1] and of Jensen[2] that an active organ like the heart maintains its normal glycogen content even after fifteen days of starvation.

In the various discussions on the subject of glycogen it has been shown that in starvation, and after protein and sugar ingestion, there is glycogen present in the body—a constant supply always ready for emergencies, which can be reduced through exercise, but which is only to be completely removed by tetanic convulsions (pp. 107 and 457).

The writer has here avoided the discussion of a production of sugar from fat. To his mind the evidence is against such production, as will be demonstrated in the chapter on Diabetes.

THE INTERMEDIARY METABOLISM OF CARBOHYDRATE

The chemical transformations of sugar molecules present a fascinating field for the explorer. It is only possible to indicate here some of the scientific facts which are leading to a correct understanding of the subject. There is some unavoidable repetition of the facts presented in the chapter on The Intermediary Metabolism of Protein.

Lobrey de Bruyn and van Eckenstein[3] found that when glucose solutions contained mere traces of hydroxyl ions, d-mannose, d-fructose, and d-pseudo-fructose appeared, and this phenomenon, called *mutarotation*, continued until the solution no longer rotated polarized light. Other hexoses have since been discovered in the mixture. According to Nef[4] any ordinary hexose can yield 116 different substances. Of these, he was able to identify 93, of which 47 were sugars

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[1] Külz: "Festschrift zu Ludwig," 1891, p. 109.

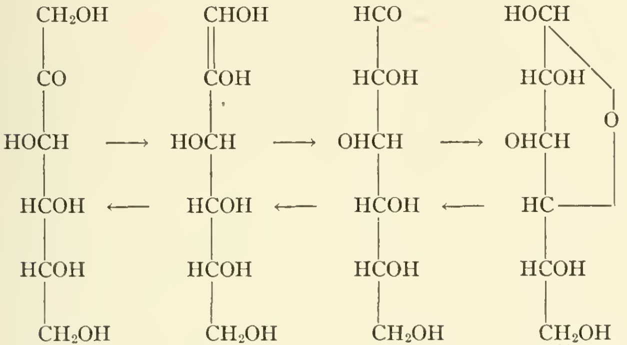
[2] Jensen: "Zeitschrift für physiologische Chemie," 1902, xxxv, 525.

[3] Lobrey de Bruyn and van Eckenstein: "Receuil des travaux chimiques des Pay-Bas," 1895, xiv, 158, 203; 1899, xix, 1.

[4] Nef: "Annalen der Chemie und Pharmacie," 1907, ccclvii, 214.

and the rest fragments of sugar cleavage. Henderson[1] finds a slow but unmistakable loss of optical activity in a glucose solution maintained at the body temperature and at the alkalinity of the blood, though the quantity of sugar present is not affected.

Nef[2] suggests that the reaction d-fructose ⟶ glucose must take place through the intermediary formation of an enol. This may be written as follows:



d-Fructose. Enol form. d-Glucose. d-Glucose.[3]

Glucose behaves like a very weak acid. In the presence of alkali, mutarotation with the production of various isomeric forms is possible. The presence of traces of acid prevents these transformations as well as any oxidative changes. To the invulnerability of the glucose molecule under these circumstances has been ascribed its non-destruction in diabetes (see p. 485). An increase in the hydrogen ion concentration of a perfusing fluid greatly reduces the utilization of glucose by an excised beating heart.[4]

The analogy between the phenomenon of Lobrey de Bruyn and the reactions which take place in the body is incomplete in that the latter always occur in one direction. Glucose, for example, is not converted into fructose within the organism.

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[1] Henderson, L. J.: "Journal of Biological Chemistry," 1911, x, 3.

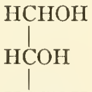
[2] Nef: "Annalen d. Chemie und Pharmacie," 1907, ccclvii, 294.

[3] Tollen's formula, accepted by Emil Fischer: "Berichte der d. chem. Gessellschaft," 1912, xlv, 461.

[4] Rona and Wilenko: "Biochemische Zeitschrift," 1913–14, lix, 173.

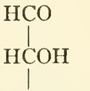
Nef believes that the many chemical reactions of sugar may be best explained on the assumption that the sugar is in part dissociated, giving residues which may be synthesized into glucose again. Such substances might be glyceric aldehyd or methylglyoxal (see p. 193). Fragments of this sort might be open to ready oxidation in the body, or be for use as the food of yeast cells in alcoholic fermentation. When glucose or its hypothetic cleavage products, glyceric aldehyd or methylglyoxal, are treated with alkali in the presence of oxygen they are oxidized to carbon dioxid and water. If no oxygen is present, lactic acid appears in the solution. But if lactic acid be added to an oxygenated alkaline solution of glucose, lactic acid is not destroyed. Hence, in the oxidative destruction of glucose, lactic acid in not an intermediary product.[1]

The relations between the *trioses* or sugars containing three carbon atoms and substances into which they are convertible are shown below. All of these substances when given to a phlorhizinized dog are completely converted into glucose:



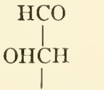
$$\begin{array}{c}\mathrm{HCHOH}\\ |\\ \mathrm{HCOH}\\ |\\ \mathrm{HCHOH}\end{array}$$

Glycerol (alcohol).



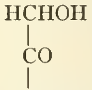
$$\begin{array}{c}\mathrm{HCO}\\ |\\ \mathrm{HCOH}\\ |\\ \mathrm{HCHOH}\end{array}$$

d-Glyceric aldehyd (aldose).



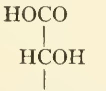
$$\begin{array}{c}\mathrm{HCO}\\ |\\ \mathrm{OHCH}\\ |\\ \mathrm{HCHOH}\end{array}$$

l-Glyceric aldehyd (aldose).



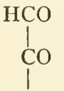
$$\begin{array}{c}\mathrm{HCHOH}\\ |\\ \mathrm{CO}\\ |\\ \mathrm{HCHOH}\end{array}$$

Dioxyacetone (ketose).



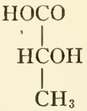
$$\begin{array}{c}\mathrm{HOCO}\\ |\\ \mathrm{HCOH}\\ |\\ \mathrm{HCHOH}\end{array}$$

d-Glyceric acid.



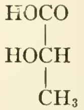
$$\begin{array}{c}\mathrm{HCO}\\ |\\ \mathrm{CO}\\ |\\ \mathrm{CH_3}\end{array}$$

Methylglyoxal.



$$\begin{array}{c}\mathrm{HOCO}\\ |\\ \mathrm{HCOH}\\ |\\ \mathrm{CH_3}\end{array}$$

d-Lactic acid.



$$\begin{array}{c}\mathrm{HOCO}\\ |\\ \mathrm{HOCH}\\ |\\ \mathrm{CH_3}\end{array}$$

l-Lactic acid.

Mandel and Lusk[2] gave lactic acid to a phlorhizinized dog and found it was eliminated as extra glucose in the urine (see p. 191). They furthermore found that the d-lactic acid

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[1] This description is taken from Woodyatt: "Well's Chemical Pathology," 2d ed., 1914, p. 578.

[2] Mandel, A. R., and Lusk: "American Journal of Physiology," 1906, xvi, 129.

which is eliminated in the urine of dogs poisoned with phosphorus disappears from such urine after the administration of phlorhizin. They, therefore, concluded that lactic acid arose from the metabolism of glucose, and that when glucose, its antecedent substance, was removed by phlorhizin, lactic acid vanished from the urine. They proposed the following formula of carbohydrate metabolism:

$$\text{lactic acid} \rightleftarrows \text{glucose} \rightleftarrows \text{glycogen}$$

Embden[1] had previously shown that d-lactic acid arises through the artificial perfusion of a liver which is rich in glycogen.

Von Fürth[2] has confirmed this work by demonstrating that the quantity of lactic acid eliminated in phosphorus-poisoning is increased after administering glucose. He further showed that the lactic acid elimination which occurs after cooling rabbits is increased if carbohydrate be ingested, and is prevented if the animal be freed from carbohydrate by means of adrenalin. He, therefore, concludes that lactic acid unquestionably arises from glucose.

Of similar import are the experiments of Sass,[3] who showed that when strychnin convulsions were induced in dogs rendered diabetic by pancreas extirpation, though the convulsions were more powerful than in normal animals, there was no lactic acid formation.

d-Lactic acid is always found in the normal blood and muscle. Von Fürth[4] states that there are between 350 and 550 milligrams of lactic acid in 100 grams of fresh normal muscle of man, horse, dog, and ox.

When a muscle dies either through heat or natural rigor mortis, lactic acid is produced from carbohydrate within the muscle. Carbon dioxid is driven out at the same time, on

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[1] Embden: "Centralblatt für Physiologie," 1904, xviii, 832.

[2] von Fürth: "Biochemische Zeitschrift," 1914, lxiv, 131; *Ibid.*, 156.

[3] Sass: "Zeitschrift für experimentelle Pathologie und Therapie," 1914, xv, 370.

[4] von Fürth: "Biochemische Zeitschrift," 1915, lxix, 199.

account of the acid production.[1] Parnas and Wagner[2] noticed that mechanical damage to frog's muscle caused the formation of lactic acid without a decrease in the carbohydrate content. This appears to confirm the lactacidogen theory of Embden[3], who found that a press juice derived from muscle formed lactic acid apparently from some unknown compound, though it left untouched added glucose, glycogen, or d-l-alanin. This substance is very likely methylglyoxal.[4] Perhaps much of the lactic acid found in tissue is formed postmortem from methylglyoxal.

Levene has accomplished a large amount of work upon the intermediary metabolism of carbohydrate. He[5] reported that leukocytes suspended in a Henderson phosphate mixture containing glucose induced glycolysis with the formation of d-lactic acid only, and without evidence of oxidation. This work has been confirmed by others,[6] who have shown that glycolysis in the shed blood is nothing more than the conversion of glucose into lactic acid. Oppenheimer[7] reports a rapid formation of d-lactic acid when d-fructose is added to a perfusing fluid and passed through a surviving liver.

Levene and Meyer[8] found further that leukocytes formed lactic acid from d-glucose, d-mannose, and d-galactose, and that kidney tissue caused a formation of lactic acid from d-glucose, d-fructose, and d-mannose.

The reactions which lead to the production of d-lactic acid from the various hexoses necessitate the presence of an intermediate substance, otherwise d-l-lactic acid would frequently be the end-product.

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[1] Fletcher and Brown: "Journal of Physiology," 1914, xlviii, 177.

[2] Parnas and Wagner: "Biochemische Zeitschrift," 1914, lxi, 387.

[3] Embden, Kalberlah, and Engel: *Ibid.*, 1912, xlv, 45; Embden, Griesbach, and Schmitz: "Zeitschrift für physiologische Chemie," 1914–15, xciii, 1.

[4] Neuberg: "Biochemische Zeitschrift," 1913, xlix, 505.

[5] Levene and Meyer: "Journal of Biological Chemistry," 1912, xi, 361; 1912, xii, 265.

[6] Kraske: "Biochemische Zeitschrift," 1912, xlv, 81; Kondo: *Ibid.*, p. 88; von Noorden, Jr.: *Ibid.*, 94.

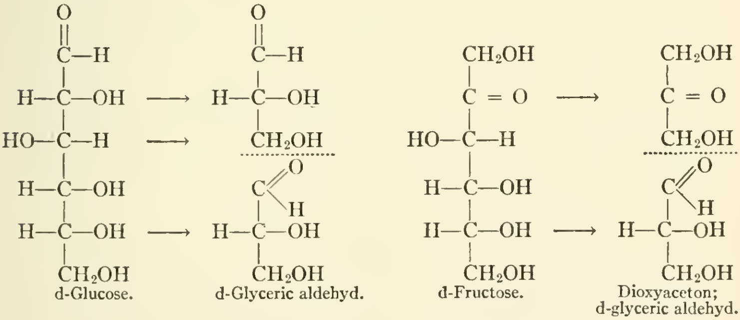
[7] Oppenheimer: "Biochemische Zeitschrift," 1912, xlv, 30.

[8] Levene and Meyer: "Journal of Biological Chemistry," 1913, xiv, 149, and *ibid.*, xv, 65.

Wohl[1] refers to the fact that methylglyoxal in alkaline solution is convertible into lactic acid. This has been shown to take place in tissue by Dakin[2] and by Neuberg,[3] and to be induced by white blood-cells.[4]

The three trioses, d- and l-glyceric aldehyd and dioxyacetone, yield lactic acid when treated with alkali.[5] When the red blood-cells of cattle are brought into a glucose solution they have no glycolytic effect; however, they do change d-l-glyceric aldehyd and dioxyacetone into d-l-lactic acid.[6] Solutions of these cells have no effect on glucose, but convert d-l-glyceric aldehyd into d-l-lactic acid. This suggests the possibility of glyceric aldehyd being an intermediate metabolite of glucose.

Embden[7] has especially emphasized this method of sugar metabolism, and pictures the cleavage of glucose and fructose as follows:



One may also conceive of the breakdown of glucose into one molecule of glyceric aldehyd and one of methylglyoxal, or into two molecules of methylglyoxal, as shown below:

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[1] Wohl: "Biochemische Zeitschrift," 1907, v, 45.

[2] Dakin and Dudley: "Journal of Biological Chemistry " 1913, xiv, 155.

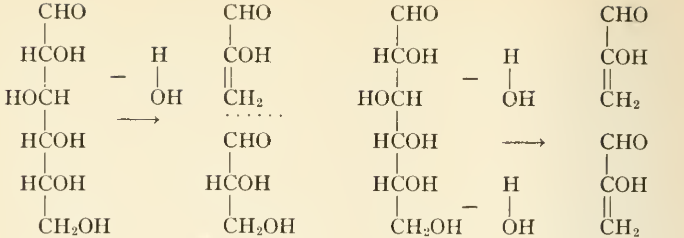
[3] Neuberg: "Biochemische Zeitschrift," 1913, xlix, 502.

[4] Levene and Meyer: "Journal of Biological Chemistry," 1913, xiv, 551.

[5] Oppenheimer: "Biochemische Zeitschrift," 1912, xlv, 134.

[6] Embden, Baldes, and Schmitz: *Ibid.*, 1912, xlv, 108.

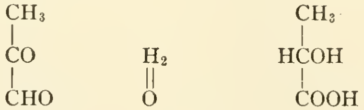
[7] Embden, Schmitz, and Wittenberg: "Zeitschrift für physiologische Chemie," 1913, lxxxviii, 210.



d-Glucose. Methylglyoxal. d-Glyceric aldehyd. d-Glucose. Methylglyoxal.

The production of methylglyoxal ($CH_3.CO.CHO$ or $CH_2:COH.CHO$) as an intermediary metabolite of sugar metabolism is of theoretic importance as showing by what means the asymmetry of the central carbon atom of a triose like d-l-glyceric aldehyd may be abolished, and then through the determinative influence of living cells be transmuted into a d-compound (Dakin, see p. 193).

It will be shown later that lactic acid appears in the urine in many asphyxial conditions (see p. 422), and the long series of experiments which have been very briefly referred to above have been performed under asphyxial conditions.[1] Only under these circumstances can the Cannizzaro reaction (see p. 192) take place.



Methylglyoxal. Lactic acid.

The experiments described above indicate that lactic acid is not oxidized when formed. It is, therefore, highly probable that it must first be synthesized to glucose, or at least undergo reversible conversion into methylglyoxal which is convertible into glucose (see p. 193) before it can undergo oxidation.

After consideration of all the evidence at hand, Dakin[2] presents "the construction of a crude scheme aiming at the

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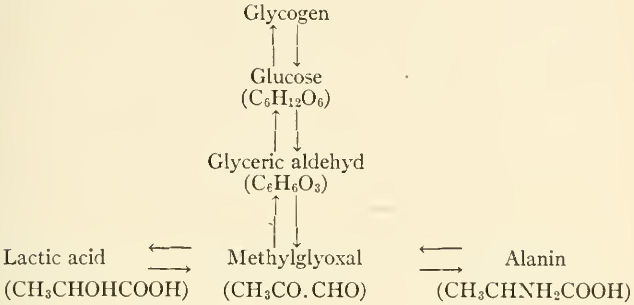
[1] Woodyatt: "Well's Chemical Pathology," 1914, p. 579.

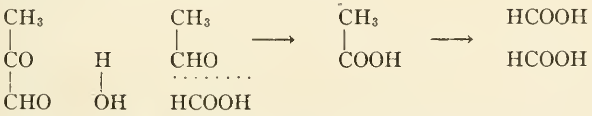
[2] Dakin: "XVIIth International Congress of Medicine," London, Subsection IIIa, 1913, p. 105.

representation of the biochemical interconversions of alanin, lactic acid, methylglyoxal, glyceric aldehyd, and glucose." (Details, pp. 192–193.)



The question of the further fate of methylglyoxal in the organism is uncertain. It is known from the work of Neuberg[1] that carboxylase, which exists within the living yeast cell, splits pyruvic acid into acetaldehyd and carbon dioxid, the acetaldehyd being then either oxidized to acetic acid or reduced to alcohol.

Levene and Meyer[2] find that leukocytes and kidney tissue will not cause the cleavage of pyruvic acid into acetaldehyd and carbon dioxid nor oxidize it either, so that when one comes to consider the ultimate fate of glucose in the organism the question is beset with difficulties, for the destruction of glucose depends on oxidative processes which take place within the living cell and which are not to be reproduced without the living structure. One can only formulate a hypothesis that acetaldehyd is a cleavage product of carbohydrate, as, indeed, was postulated by Magnus-Levy[3] while working in Hofmeister's laboratory. From methylglyoxal, acetaldehyd might arise as follows:



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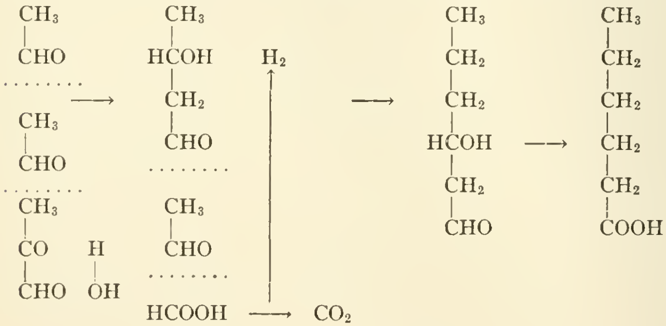
[1] Neuberg: "Biochemische Zeitschrift," 1911, xxxvii, 170.
[2] Levene and Meyer: "Journal of Biological Chemistry," 1914, xvii, 443.
[3] Magnus-Levy: "Archiv für Physiologie," 1902, p. 365.

In the presence of oxygen acetaldehyd would be oxidized to acetic acid, which is not convertible into glucose, and this would then be oxidized to formic acid which readily breaks up into carbon dioxid and water (see p. 302). In the presence of hydrogen, acetaldehyd is reduced to alcohol.

$$\begin{array}{c} CH_3 \\ | \\ CHO \end{array} + H_2 \longrightarrow \begin{array}{c} CH_3 \\ | \\ CH_2OH \end{array}$$

This, however, cannot take place to any considerable extent in the organism, for in asphyxial conditions lactic acid is the end-product of glucose breakdown, and from it alcohol cannot be evolved. The production of alcohol from carbohydrate in metabolism is thus automatically checked.

The formation of fat from carbohydrate when it is given in excess is probably due to the condensation of aldehyd molecules (Magnus-Levy). The process may thus be pictured:



If at any time the aldehyd radicle at the end of the chain becomes oxidized, the fatty acid is completed and the process of addition terminates. In this fashion through condensation of acetaldehyd radicles split from methylglyoxal, fatty acids with even numbers of carbon atoms may be synthesized from carbohydrate in the animal organism.

Written in its simplest form the production of palmitic acid from glucose would appear as follows:

$$4C_6H_{12}O_6 = C_{16}H_{32}O_2 + 2HCOOH + 6CO_2 + 6H_2O$$

The end-result is one of carbon dioxid cleavage, just as in the case of the alcoholic fermentation of pyruvic acid induced by yeast cells.

To enter still deeper into the part played by yeast cells, and to discuss in detail the notable and fascinating work of Carl Neuberg, would carry one beyond the object of this book.[1]

The various sugars diffuse rapidly in the body. Thus when milk-sugar, which cannot be oxidized by the organism, is introduced intravenously into a dog, after half an hour 75 per cent. of the quantity present in the animal is found in the tissues and only 25 per cent. in the blood.[2] The entrance of glucose into the cells by diffusion is accelerated by increasing their temperature.[3]

THE INFLUENCE OF CARBOHYDRATE ON PROTEIN METABOLISM AND PROTEIN RETENTION

At the suggestion of Voit, who believed that the sudden withdrawal of carbohydrate from the food would increase protein metabolism and would explain the high tissue waste in diabetes, Lusk[4] established himself in nitrogen equilibrium at two different levels. Withdrawal of 350 grams of carbohydrate from the diet increased the protein metabolism as appears below. The losses of body nitrogen are greater for the second day of change in the diet than for the first, since the metabolism at first remains under the influence of an ample glycogen supply which is available as a source of carbohydrate (see p. 72).

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[1] Consult Neuberg: "Oppenheimer's Handbuch der Biochemie," Ergänzungsband, 1913, p. 569; Neuberg: "Biochemische Zeitschrift," 1915, lxxi, 1; v. Euler: "Neure Forschung über alkoholische Gährung, Fortschritte der Naturwissenschaftlichen Forschung," 1914, x, 63.

[2] Schwarz and Pulay: "Zeitschrift für exp. Path. und Ther.," 1915, xvii, 383.

[3] Masing: "Pflüger's Archiv," 1914, clvi, 401.

[4] Lusk: "Zeitschrift für Biologie," 1890, xxvii, 459.

INFLUENCE OF CARBOHYDRATE WITHDRAWAL ON PROTEIN METABOLISM

Exp. No.	Days of Experimentation.	Food.		Excreta N.	±N to Body.	Remarks.
		Calories.	N.			
I	1, 2, 3	2953	20.55	19.84	+0.71	With carbohydrate.
	1	1078	20.55	23.78	−3.23	Without carbohydrate.
	2, 3	1078	20.55	27.00	−6.45	Without carbohydrate.
II	2	2490	9.23	13.08	−3.85	With carbohydrate.
	1	615	9.23	13.27	−4.04	Without carbohydrate.
	2	615	9.25	17.18	−7.95	Without carbohydrate.

These results may be compared with the later results of Thomas (see p. 155), who showed that protein containing 18.4 grams of nitrogen when given to a man did not maintain the body in nitrogen equilibrium when no carbohydrate was administered.

Tallqvist[1] found that *partial* replacement of carbohydrate by fat in the diet may have no influence or only a transitory one upon the amount of protein metabolized. Thus, after establishing nitrogen equilibrium in man with a diet containing about 16 grams of nitrogen, 10 per cent. of the calories being in protein and 90 per cent. in carbohydrate, he replaced one-third of the carbohydrate calories with an isodynamic quantity of fat and obtained nitrogen equilibrium on the third day of the diet. This is of value in practical dietetics.

Zeller[2] gave to a man a daily diet which contained very little protein and between 2700 and 3300 calories divided into different percentages of carbohydrate and fat. The protein metabolism of the body was not significantly altered until less than 10 per cent. of the total calories were given in the form of carbohydrate, *i. e.*, butter, 360 grams; sugar, 70 grams; sauerkraut, 300 grams; tomatoes, 100 grams, containing 3300 calories. At this juncture, when, as Zeller notes, one molecule of monosaccharid is present for two of fat in the

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[1] Tallqvist: "Archiv für Hygiene," 1902, xli, 177.

[2] Zeller: "Archiv für Physiologie," 1914, p. 213.

diet, aceton appeared in the urine in traces. When 5 per cent. of the calories were given in carbohydrate, aceton appeared abundantly in the urine, and when the whole of the diet consisted of fat calories there was a still higher aceton excretion, with an increasing ammonia production to neutralize the acid formed and the patient complained of weakness and discomfort.

The following table epitomizes the results obtained:

Food.			Urine N Grams.	Urine N per 100 Grams. N in Body Grams.
N Grams.	Calories in Per Cent.			
	Carbohydrate.	Fat.		
3.43	100	0	5.18	0.16
3.21	75	25	5.75	0.18
3.27	50	50	5.60	0.17
3.88	25	75	4.82	0.15
0.87	10	90	5.04	0.16
0.86	5	95	6.02	0.20
1.41	0	100	6.90	0.24
3.43	100	0	4.85	0.15

If two molecules of fat are oxidized in the presence of one molecule of glucose (which assumes that the 3300 calories contained in the diet were liberated in metabolism), then one molecule of fat would be oxidized in the presence of one dissociated triose molecule. Each molecule of fat is made up of one molecule of gylcerin and three of fatty acid. Since glycerin is convertible into a triose, it is apparent that from glycerin and ingested sugar two molecules of triose are available for simultaneous oxidation when three of fatty acid are burned. Besides this, a small number of triose molecules may be derived from protein metabolized and another quota from stored glycogen. It appears from this analysis *possible* that the normal combustion of fat each molecule of β-oxybutyric acid, which is the end-product of the oxidation of each fatty acid, requires the presence of a triose molecule. Under these conditions the oxidation of fat would take place without acidosis and without increasing the metabolism of protein.

It is too early as yet to give a satisfactory explanation of the chemical reactions which might accompany this phenomenon. It may be noted that when protein is given in large quantity with fat the acidosis does not appear. This is understandable in view of the production of glucose from protein. One may also marvel at the fact that the "bread cards" issued in Vienna during the great war for 50 grams of bread daily per inhabitant can yield scarcely sufficient carbohydrate to prevent the occurrence of acidosis were bread the only food.

Zeller's experiments verify the conclusion that when the protein metabolism is reduced to a minimum, the elimination of creatinin nitrogen constitutes about 20 per cent. of the total quantity of urinary nitrogen (see p. 209).

A significant fact is that when the body changes from a carbohydrate diet to one of fat or protein there is a considerable loss of water. This was first noted by Bischoff and Voit,[1] who gave bread to a dog forty-one days and witnessed a loss in body weight of 531 grams, although if the nitrogen elimination of the period had been all attributed to muscle breakdown the loss in body weight should have been over 3700 grams. Then when 1800 grams of meat were given in quantity sufficient to cause protein deposit, the weight of the animal fell 310 grams on the first day of this diet.

The phenomenon also occurs in man, as the following experiment of Benedict and Milner[2] demonstrates. The experimental period lasted six days, mechanical work was performed daily, and isodynamic quantities of food, which were somewhat under the needs of the body, were ingested. During the first three days 66 per cent. of the energy in the food was contained in carbohydrates, and during the last three

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[1] Bischoff and Voit: "Gesetze der Ernährung des Fleischfressers," 1860, pp. 211 and 214.

[2] Benedict and Milner: "U. S. Dept. of Agriculture," Office of Experiment Stations, 1907, Bull. 175, p. 224.

days 67 per cent. of the energy was in the form of fat. The following changes were noted:

	CARBOHYDRATE DIET.	FAT DIET.
Daily change water content of body, grams	+165	−906
Daily change in body weight, grams	+ 61	−914

A loss of body glycogen is, therefore, associated with a loss of body weight.

If carbohydrates be ingested alone, immediately after starvation, the protein metabolism may fall below the starvation amount.

This higher protein-sparing property gives to dogs fed on carbohydrates alone a longer lease of life than is granted to those fed on fat alone, although the ultimate outcome is the same.

The protein metabolism may be reduced to one-third the fasting value, a result also obtained by Landergren[1] and by Folin[2] in man. Cathcart[3] gave a man who had been fasting fourteen days a diet of cream (300 c.c.) and starch (400 grams). The nitrogen excretion in the urine was as follows:

	TOTAL N.	UREA N.
Day 14 of starvation	7.78	5.99
" 1 on cream-starch diet	7.43	5.80
" 2 " "	3.58	2.29
" 3 " "	2.84	1.76

The absence of a fall in protein metabolism on the first day is probably to be explained by assuming a large deposit of glycogen within the body at the expense of the starch ingested (see p. 290). On the third day of the diet the protein metabolism had fallen to one-third that observed in fasting (see p. 280).

The sparing influence of carbohydrate oxidation upon protein metabolism has been beautifully illustrated by Landergren.[4] Diets containing carbohydrates and fats, but scarcely

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[1] Landergren: "Skan. Archiv für Physiologie," 1903, xiv, 112.
[2] Folin: "American Journal of Physiology," 1905, xiii, 45.
[3] Cathcart: "Biochemische Zeitschrift," 1907, vi, 109.
[4] Landergren: *Loc. cit.*,

any nitrogen (about one gram daily), were given men and the protein metabolism noted. This condition is called that of *specific nitrogen hunger*. After four days' administration of such a diet the urinary nitrogen may be reduced to less than 4 grams.

In one experiment in which this was accomplished carbohydrates were entirely replaced by fat, with the result that protein metabolism rose to the amount found in starvation (about 10 grams). It has already (p. 248) been explained that ingestion of fat alone will not reduce protein metabolism below that of starvation. The experiment is as follows:

	Carbohydrate Period. Diet = 45.2 Cal. per Kg. N in Urine.
Day 0	12.76*
" 1	....
" 2	....
" 3	....
" 4	3.76

	Fat Period. Diet = 43.7 Cal. per Kg. N in Urine.
Day 5	4.28
" 6	8.86
" 7	9.64

* Ordinary diet.

On day 5, the first of the fat diet, it is evident that the protein metabolism was affected by the use of the glycogen supply of the body, an influence which became negligible on the second and third days of the fat diet (p. 72).

Landergren gives the following results in various cases of specific nitrogen hunger, showing the nitrogen in the urine before the diet and after four days thereof:

	II.	III.	IV.	V.
N in urine (ordinary diet)	12.76	11.87	13.7	15.2
N in urine (specific N hunger)	3.76	3.95	3.04	4.2
Calories in diet per kg	45.2	37.8	45.0	38.4

This reduction of protein metabolism to 4 grams on the fourth day was brought about by the following diets in the different cases:

II. 750 g. carbohydrates = 45.2 cal. per kg.
III. 300 g. carbohydrates + 150 g. fat = 37.8 " "
V. 380 g. carbohydrates + 150 g. fat = 38.4 " "

A diet containing half its calories in carbohydrates and half in fat has therefore the same protein protecting power as one made up of carbohydrates alone. This demonstrates the rationality of a mixture of the non-nitrogenous food-stuffs.

The experiments of Karl Thomas have shown the prolonged influence of a previous high protein diet upon the nitrogen output in the urine of man. A starch-cream diet had reduced the urinary nitrogen elimination to 2.2 grams daily. Then, during four days, 76, 87, 85, and 71 grams of nitrogen were given in the diet. The nitrogen retention in the body for the first four days was +43, +25, +8, and −10 grams, a total of +66 grams. This stored protein was by no means as rapidly demolished in the body as it was added to it. This appears in the third column of the following table:

THE INFLUENCE OF PREVIOUS PROTEIN INGESTION UPON THE EXCRETION OF NITROGEN IN GRAMS IN MAN WHEN A DIET OF FAT AND CARBOHYDRATE IS ADMINISTERED.

		Landergren.[1]	Kinberg.[2]	Thomas.[3]
Last normal day		12.8	25.2	77.7
Specific N hunger day	1	8.9	18.3	28.3
	2	5.2	14.5	10.7
	3	4.3	11.6	5.1
	4	3.8	9.1	5.2
	5	...	8.0	4.7
	6	...	7.3	4.2
	7	...	5.6	3.9
	19	...	...	2.2
Meat (2.9 gm. N)	20	...	...	2.2

Rubner[4] has defined the minimal protein metabolism under conditions of administration of carbohydrate in excess, as the "wear-and-tear" quota of protein metabolism. This minimal level is only achieved after the reduction of the cells from their optimal protein condition through loss of body nitrogen. Rubner estimates that a kilogram of body weight

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[1] Landergren: *Loc. cit.*

[2] Kinberg: "Skan. Archiv f. Physiologie," 1911, xxv, 291.

[3] Thomas: "Archiv f. Physiologie," 1910, Suppl., p. 249.

[4] Rubner: "Archiv für Hygiene," 1908, lxvi, 45.

contains 30 grams of nitrogen. Since the individual investigated by Thomas weighed 73 kilograms, he contained 2190 grams of nitrogen. When given 89 grams of protein nitrogen on a single day this represented 4.5 per cent. of his body's supply. The 66 grams of protein nitrogen stored during the days of liberal protein ingestion, which raised the cells to an optimal condition, represented 3 per cent. of the total protein content. When carbohydrates alone were given this stored protein was only gradually eliminated—there was a *transition period* of constantly diminishing protein waste until a minimum of 2.2 grams of urinary nitrogen (with 0.6 grams in the feces) was found. The urinary nitrogen then represented approximately 1 part in 1000 of protein contained in the organism. This is the lowest "wear-and-tear" quota of protein metabolism.

It is a point of debate whether the "stored protein" becomes true living tissue protein or whether it represents a special variety of deposit protein, which is retained in the tissue cells very much as glycogen is retained by them (see p. 81). The storage takes place largely in the liver.[1] It would be interesting to follow the sulphur excretion during the early days of the transition period from high to low protein metabolism and note whether this sulphur elimination runs parallel to that of nitrogen in the usual ratio (see p. 169). Should this be the case it would indicate that "deposit protein" was the same as tissue protein. Phosphorus retention is not always present during the period of protein deposit (see p. 287).

Rubner has given further useful definitions. A "repair quota" of protein is required in the food in order to replace that lost in the "wear and-tear" quota. A "growth quota" of protein is necessary in addition to a repair quota under the circumstances of multiplication of cells and of developing protoplasm in the young. Furthermore, an "improvement quota" of protein may be necessary in the adult after wasting disease, or after fasting, in order to bring the cells to an opti-

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[1] Tichmeneff: "Biochemische Zeitschrift," 1914, lix, 326; Cahn-Bronner: *Ibid.*, 1914, lxvi, 289.

mum of protein condition, thereby improving the welfare of the living organized protein.[1] When protein is given in excess so that it is not used for repair nor for growth nor deposit, its constituent amino-acids are deaminized and the residual oxy- or keto-acids are in part converted into glucose, in part into fatty acid, thus yielding fuel to the cells just as would carbohydrate and fat. This fraction of protein Rubner designates as the "dynamic quota."

Thomas calculated that during the period of minimal "wear-and-tear" protein metabolism, 0.4 calories were derived from the metabolism of 1.5 milligrams of protein per kilogram of body weight every hour, while 0.96 calories were derived from the oxidation of 259 milligrams of glucose. In other words, protein furnished only 4 per cent. of the energy required by a man at rest. Since mechanical work scarcely influences the "wear-and-tear" quota of protein metabolism (see p. 311), although it largely increases the oxidation of carbohydrate, it is evident that protein may play a very small rôle as a producer of energy for the maintenance of the function of life.

When carbohydrates are given in the diet, it is possible to establish *nitrogen equilibrium* at a much lower level than when protein alone or protein and fat are ingested.

When carbohydrates and protein are ingested together in quantity sufficient for the requirement of the organism, it has been found that, taking the starvation protein metabolism as one, nitrogen equilibrium can be maintained by ingesting one part of protein.[2]

The work of Sivén,[3] however, was the first indication that nitrogen equilibrium may be maintained at even a lower level than that ordinarily present in starvation. A somewhat undersized healthy man, weighing 60 kilograms, who normally ate a mixed diet containing 16 grams of nitrogen, was given less and less protein, and an attempt was made to establish

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[1] Rubner: "Archiv für Physiologie," 1911, p. 67.

[2] E. Voit and Korkunoff: "Zeitschrift für Biologie," 1895, xxxii, 117.

[3] Sivén: "Skan. Archiv für Physiologie," 1900, x, 91.

nitrogen equilibrium at lower and lower levels. The daily ration was rich in carbohydrates and yielded 2444 calories.

The experiment was divided into four periods of about a week each, which may be summarized as follows:

Length in Days.	N in the Food.	Days Until N Equilibrium was Obtained.	N Loss Before N Equilibrium was Obtained.	Total N Added to Body.
I, 7	12.69	1	0.53	+9.73
II, 8	10.40	1	0.34	+6.04
III, 6	8.71	at once	....	+4.39
IV, 6	6.26	3	2.09	−0.58

It is apparent that nitrogen equilibrium may be established after ingesting 6.26 grams of nitrogen, although, as has been seen, the elimination during the early days of starvation in man is usually 10 grams. During the first three periods of reduced protein intake, as much as 20.16 grams of protein nitrogen were actually added to the body. In a fifth period nitrogen equilibrium was obtained on the fourth day on a diet containing 4.52 grams of nitrogen.

Thomas[1] administered during frequent intervals small quantities of meat washed free from extractives to the man who had partaken of a starch-cream diet and had reduced his protein metabolism to one represented by a minimum of 2.2 grams of urinary nitrogen daily. Nitrogen equilibrium was nearly achieved after administration of that quantity of protein nitrogen which corresponded to the quantity eliminated in the urine and feces. This is shown below in grams per day:

Day.	49	50	51	52	53	54	55
N in diet	0	0	2.89	2.89	2.61	2.61	0
N in urine	2.31	2.16	2.23	2.48	2.56	3.13	3.49
N in feces	0.74	0.73	0.74	0.73	0.74	0.73	0.74
N loss	−3.05	−2.89	−0.08	−0.32	−0.69	−1.25	−4.23

In this experiment the ingestion of the quantity of protein which was the equivalent of the "wear-and-tear" quota was

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[1] Thomas: "Archiv für Physiologie," 1910, Suppl., p. 249.

at first nearly sufficient to completely "repair" the tissue. While living upon this low protein diet the mental and muscular power was unchanged.

Chittenden[1] finds that nitrogen equilibrium may be maintained on a diet containing a very small amount of protein and two-thirds of the body's requirement of energy. The first experiment was on Fletcher and lasted six days. The daily ration contained 7.19 g. nitrogen + 38.0 g. fat + 253 g. carbohydrates = 21.3 calories per kilogram. The excreta contained 6.90 grams of nitrogen daily. On this diet the individual showed "remarkable physical strength and endurance."

Another experiment was performed by Chittenden on himself and lends itself for interesting comparison with the results of the ingestion of a maintenance ration. The food was principally vegetable. The results may be thus tabulated:

A LOW LEVEL OF NITROGEN EQUILIBRIUM IN NORMAL AND UNDERNUTRITION

Date.	Diet.		N Excretion.	N Balance.
	N in Grams.	Cal. per Kg.		
March 23..........	6.70	34.7	6.56	+0.23
March 25..........	6.88	22.4	6.34	+0.54

Nitrogen equilibrium may therefore be maintained at a low level, even during the state of undernutrition present when 22.4 calories per kilogram are in the daily diet. On a milk diet Rubner[2] found that the ingestion of 2483 grams of milk containing 84 grams of protein and two-thirds the body's requirement of energy resulted in the addition of 6.7 grams of protein to the body daily for three days (see p. 353).

It is a valuable piece of information to know that one may diet an obese patient on a food containing little protein and two-thirds the body's energy requirement without danger of

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[1] Chittenden: "Physiological Economy in Nutrition," 1904, pp. 14, 40.

[2] Rubner: "Zeitschrift für Biologie," 1879, xv, 130.

protein loss. The other third of the necessary energy will be furnished by the body's own store of fat. It is not remarkable that the body is capable of great physical effort on such a diet, for a fasting man is also competent in this direction (see p. 71).

In Chapter on p. 156 mention was made of the sparing action of gelatin on protein metabolism, and its ingestion was found to prevent about 23 to 37.5 per cent. of the protein loss during starvation. Murlin[1] in an extensive series of experiments has shown that the sparing power of gelatin is greater than this when it is ingested with a mixed diet. He finds that if the quantity of nitrogen eliminated in fasting be taken as one, then nitrogen equilibrium may be maintained in dogs and in man on ingestion of a diet rich in carbohydrates, whether the nitrogen of the diet be protein nitrogen equal to one or whether it contain one-third protein plus two-thirds gelatin nitrogen. This is shown in the following experiment on a man, the results being expressed in averages per day:

EFFECT OF ADMINISTERING GELATIN IN A MIXED DIFT IN MAN

N elimination on a third day of fasting = 13.23 gm.

Source of N in Diet.	No. of Days.	Cal. in Food.	Cal. per Kg.	N in Food.	N in Excreta.	N to Body.
				Grams.	Grams.	Grams.
All protein N	3	3208	47	14.25	13.33	+0.87
Two-thirds (63%) gelatin N + one-third protein N	2	3620	51	14.53	13.82	+0.71
All protein N	2	3220	46	14.26	13.52	+0.74

Murlin[2] also showed that the sparing power of gelatin was due to its immediate chemical nature, and not to the 60 per cent. of glucose which can arise from it in metabolism (see p. 174). For example, a fasting dog was given 12 grams of glucose daily for four days after thirteen days of fasting; then 20 grams of gelatin were substituted during a period of four days. The glucose scarcely exerted any sparing power over

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[1] Murlin: "American Journal of Physiology," 1907, xix, 285.

[2] Murlin: *Ibid.*, 1907, xx, 234.

the protein metabolism, whereas the ingestion of gelatin showed the usual sparing of 31 per cent.

The same fact was demonstrated on a man who was brought into nitrogen equilibrium on an adequate mixed diet containing 10 grams of nitrogen and carbohydrates enough to supply 50 per cent. of the energy. The state of nitrogen equilibrium was not quite maintained when gelatin was used as the source of two-thirds of the nitrogen in the diet. Murlin explained this as being due to a dislike for sweets on the part of the individual so that he could not take carbohydrates in large excess. However, when the nitrogen of the diet was reduced so as to contain only protein nitrogen equal to one-third that eliminated in fasting, together with the 60 per cent. of glucose which could have originated from the gelatin previously ingested, the waste of body nitrogen rose far above that observed when gelatin and other protein were given. The experiment may thus be presented:

INFLUENCE OF GELATIN IN METABOLISM

Figures are for the last day of each period

Source of N in Diet.	No. of Days.	Cal. in Food.	Cal. per Kg.	N in Food.	N in Excreta.	N to Body.
				Grams.	Grams.	Grams.
Meat + veg. protein N*.....	4	1971	43	10.05	10.35	−0.30
Two-thirds (67%) gelatin N+one-third veg. protein N	6	1935	42	9.62	10.12	−0.50
One-third veg. protein N...	3	1858	40	3.23	5.62	−2.39

* Two-thirds meat N + one-third vegetable N in wheat, oats, and rice.

Here the rise in the metabolism of body protein corresponds to the withdrawal of gelatin from the diet even in the presence of a considerable intake of carbohydrate. Hence Landergren's[1] interpretation that the rise in nitrogen elimination, which takes place on changing from a pure carbohydrate to a pure fat diet, is due to the body's absolute requirement for carbohy-

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[1] Landergren: Inaugural Dissertation, 1902: "Maly's Jahresbericht," 1902, p. 685.

drate and that it obtains this by increasing its protein metabolism is scarcely tenable, although even now this point is emphasized by many writers.

It is evident that the "wear-and-tear" quota of protein metabolism must be covered by the ingestion of an equal "repair" quota, while the additional "dynamic" quota may be supplied by protein or by gelatin. Murlin found that the "repair" quota was best administered in the form of beef heart, and that the proteins of biscuit meal were very inefficient as sparers of body protein.

In the course of his experiments Murlin found that the longer the animal had fasted, that is, the lower its protein condition, the more readily did gelatin reduce the waste of body protein.

Murlin also showed that three-quarters of the starvation nitrogen ingested as gelatin and one-quarter as protein were not able to maintain nitrogen equilibrium in the dog. Two-thirds the starvation nitrogen requirement ingested as gelatin and one-third as protein maintain nitrogenous equilibrium. Carbohydrates ingested alone reduce protein metabolism to one-third that found in starvation. One-third the starvation quantity seems to be the lower limit of protein metabolism compatible with life.

It may also be noted that in a fasting diabetic dog the protein metabolism may rise to fivefold that noted in simple fasting (see p. 463), or fifteenfold the *irreducible minimum* of the "wear-and-tear" quota. Under these circumstances the writer has found that pure gelatin given alone is more effective as a protein sparer than it is in simple fasting. Thus after giving 30 grams of gelatin to a fasting phlorhizinized dog the following results were obtained on analyzing the urine every twelve hours:

	Glucose.	N.	Body N.
Fasting, twelve hours	12.58	3.77	−3.77
Gelatin (= 4.644 g. N), twelve hours	20.66	6.02	−1.37
Fasting, twelve hours	.....	3.79	−3.79

If the fecal nitrogen, which is very small after gelatin ingestion, be neglected, it may be calculated that body protein was spared to the extent of 63.7 per cent. after the administration of gelatin instead of 30 per cent. as in ordinary fasting. One may, therefore, conclude that the great waste of body protein which takes place in diabetes belongs in Rubner's category of "dynamic" protein metabolism, for which gelatin may be largely used as a substitute.

McCollum[1] gave to a pig a diet of starch and salts containing 90 calories per kilogram of body weight for twenty-four days and then during eight days added gelatin, the nitrogen content of which equalled the urinary nitrogen excretion at the end of the starch period. The results showed a sparing of the minimal endogenous protein metabolism (the "wear-and-tear" quota) equal to 40 per cent., as appears below:

	N in Diet.	Urine N.	Feces N.	Total N.	Loss to Body.
Starch diet, twenty-fourth day.	0	2.59	0.94	3.53	−3.53
Starch + gelatin, average of eight days.	2.62	3.72	1.04	4.76	−2.14

The creatinin nitrogen, which remained at the same daily level throughout the experiment, was at the start 18.3 per cent. of the total urinary nitrogen. It is interesting to note that the reduction in the amount of endogenous protein metabolism brought about by the ingestion of gelatin is exactly the same quantity which may be withdrawn from the endogenous metabolism in the form of glycocoll following the ingestion of sodium benzoate (see p. 188). The creatinin excretion is not affected in either case. It is interesting to speculate whether the exogenous amino-acids of gelatin replace in metabolism that part of the "wear-and-tear" quota which involves the endogenous production of glycocoll.

Curiously enough, the endogenous protein metabolism may be greatly reduced when ammonium acetate or citrate are

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[1] McCollum: "American Journal of Physiology," 1911–12, xxix, 215.

added to a rich carbohydrate diet. This subject was first studied by Grafe,[1] who announced that nitrogen equilibrium could be maintained with carbohydrate and ammonium acetate in the diet, and who saw in this a synthetic formation of protein within the organism. Even the ingestion of ammonium chlorid reduced the amount of protein metabolism. A paper by Abderhalden[2] followed quickly, which showed that though ammonium acetate when given with starch, sugar, fat, and bone-ash greatly reduced the endogenous metabolism, yet nitrogen equilibrium could not be attained under these circumstances. Abderhalden believes it possible that the animal cell may synthesize alanin, serin, or even cystein under these conditions, although he thinks that the heterocyclic and aromatic amino-acids are much less likely to be formed. He suggests that the mass action of ingested ammonia may prevent the deamination of some of the amino-acids, which may therefore be used once again for the repair of the tissue. Abderhalden's explanation seems the more rational of the two. A considerable sparing of endogenous protein metabolism was observed by Grafe[3] to take place after the administration of ammonium citrate with carbohydrate, and this has been confirmed by Underhill,[4] who, however, could find no influence exerted by ammonium chlorid.

Grafe[5] has announced that urea when given with carbohydrate protects body protein from waste just as ammonium citrate does. This is denied by Abderhalden.[6] Henriques and Andersen[7] explain Grafe's results as due to the growth of bacteria within the medium of the intestinal tract of herbivora.

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[1] Grafe and Schläpfer: "Zeitschrift für physiologische Chemie," 1912, lxxvii, 1.

[2] Abderhalden: *Ibid.*, 1912, lxxviii, 1. A vast literature, experimental and polemical, has arisen from these two papers.

[3] Grafe: "Zeitschrift für physiologische Chemie," 1912, lxxxii, 347.

[4] Underhill and Goldschmidt: "Journal of Biological Chemistry," 1913, xv, 341.

[5] Grafe and Turban: "Zeitschrift für physiologische Chemie," 1913, lxxxiii, 25.

[6] Abderhalden: *Ibid.*, 1913, lxxxiv, 218.

[7] Henriques and Andersen: *Ibid.*, 1914, xcii, 21.

Rats may be maintained when given such bacterial masses as the source of their protein food.

Lower organisms have the power to synthesize protein from sugar and some simple source of nitrogen. Thus, Armand-Delille[1] found that the tubercle bacillus grew as well in a culture-medium of sugar, glycerin, glycocoll, and arginin, with addition of appropriate salts, as it did in a solution of 1 per cent. of peptone in bouillon.

Delbrück, in Germany, discovered that yeast cells developed rapidly and formed body protein when they were placed in a solution of sugar and ammonium sulphate. The mass thus developed is stated to have been used on a large scale as a source of protein food for cattle during the time of fodder scarcity introduced by the present war.

Lower organisms may therefore form the various aliphatic, aromatic, and heterocyclic amino-acids from carbohydrate and ammonium salts.

Within the body of the mammal there is evidence that some of the simpler deamination reactions are reversible (see p. 194), but the experiments with gelatin demonstrate that when tryptophan and phenylalanin are lacking these important building-stones of protein cannot be synthesized, for nitrogen equilibrium can only be obtained when they are admixed with the gelatin food. The consideration of other "deficient" proteins will be given elsewhere.

The cause of the great reduction in the fasting quantity of protein metabolism when carbohydrates alone are ingested has been thus stated by Knoop:[2] "The animal body may therefore synthesize amino-acids from ammonia. If amino-acids can be produced from oxyacids, such as originate from carbohydrate metabolism, for example, then it is possible to comprehend chemically not only the production of sugar from protein but also reactions in a reverse direction. The minimal nitrogen metabolism of fasting may be reduced either through

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[1] Armand-Delille, Mayer, Schaeffer, and Terroine: "Archive de Physiologie et de Pathologie generale," 1913, xv, 797.

[2] Knoop: "Zeitschrift für physiologische Chemie," 1910, lxvii, 489.

the ingestion or through the intermediary production of non-nitrogenous acids, which unite with ammonia prior to its synthesis to urea and form amino-acids."

Since amino-acids when ingested tend to reduce protein metabolism this seems a plausible hypothesis. However, one should bear in mind the experiment of McCollum (see p. 188), in which 40 per cent. of the urinary endogenous protein nitrogen could be removed in the form of glycocoll when benzoate of soda was ingested without affecting the amount of protein metabolism. This glycocoll nitrogen when once bound as hippuric acid could not have participated in any interplay of chemical reaction with keto- or oxyacids produced in carbohydrate metabolism.

Rubner has called attention to the extremely soluble character of the monosaccharids, and it may be that a plethora of carbohydrate molecules reduces the demands upon the structural protein of the cells. Furthermore, it has been noted that the production of β-oxybutyric acid is associated with an increased protein breakdown (see p. 94), so that the action of carbohydrate may perhaps prevent chemical injury to the cellular framework by promoting the normal oxidation of β-oxybutyric acid.

Since carbohydrates so effectively spare protein from combustion, it would seem logical that their use should render the retention of protein in the body easier than when fat is given with protein.

Lüthje[1] finds a long-continued nitrogen retention in man when much nitrogen in protein is ingested (up to 50 gm. N daily!) and carbohydrates and fat making a total of 4000 calories or 66 calories per kilo. (See also Bornstein's experiment, p. 154.)

In a subsequent paper Lüthje[2] finds that the P_2O_5 retention in convalescence is that which corresponds to the retention of protein for the formation of new tissue, including bone.

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[1] Lüthje: "Zeitschrift für klinische Medizin," 1902, xliv, 22.

[2] Lüthje: "Deutsches Archiv für klinische Medizin," 1904, lxxxi, 278.

Sometimes in a healthy person not enough P_2O_5 is retained to build up "flesh," and the protein retained must, therefore, exist in the form of "deposit protein." This protein, he says, is not stored in the blood, for the composition of the blood does not alter, but is perhaps retained in the cellular fluids, just as glycogen is retained by the cells.

Rubner states that the greater the impoverishment of the protein supply in an animal fed with fat, the more powerful is the protective effect of small quantities of ingested protein over the loss of body protein. Also the retention of protein depends on the protein content of the animal as well as on the quantity of protein ingested. This is illustrated in the following table:

INFLUENCE OF THE PROTEIN CONTENT OF A DOG ON THE RETENTION OF PROTEIN INGESTED

Total N Content of Dog.	N in Terms of 100 N in Dog in Food.	to Body.
318.8	5.25	+1.65
354.7	5.57	+1.02
310.6	6.72	+2.64
363.7	12.79	+2.62

It is evident from this that of the same diet of protein more will be retained when the nitrogen content of the dog is low than when it is high; and also that a small protein intake may cause the same retention of nitrogen as a large protein intake, if in the first instance there be a relative impoverishment of the protein content of the animal.

According to these laws adult cells which have been depleted of their protein may gradually improve their nutritive condition until they reach an *optimum*, at which point they lose their power to attach additional protein.

This is also illustrated in an experiment by McCollum,[1] who gave to a pig a diet containing 14 grams of nitrogen per day in the form of casein and starch, so that the value of the diet was 100 calories per kilogram during a period of thirty-six days. The animal retained 43 per cent. of the nitrogen in-

[1] McCollum: "American Journal of Physiology," 1911–12, xxix, 215.

gested. During the first three days it added 9.65 grams of nitrogen to the body daily; during the last three, 3.69 grams. With the increase in active protoplasm the creatinin nitrogen excretion rose from 0.24 to 0.31 grams per day.

The conditions of protein metabolism are entirely similar to those of starch metabolism: (1) Digestive hydrolysis; (2) partial combustion of the end-products; and (3) possible regeneration of portions of the end-products into substances akin to the originals but characteristic of the organism—*i. e.*, glycogen and body proteins. In the case of proteins the second or metabolic process involves the production of sugar and of fatty acids from the amino-acids involved. The third or regenerative process is promoted by such a protein as casein, which yields the proper variety of cleavage products.

In conclusion, it may be said that carbohydrates are the most economical of the food-stuffs, both physiologically and financially. They are the greatest sparers of protein. Ingestion of fat has for its object the relieving of the intestine from excessive carbohydrate digestion and absorption. Ingestion of fat in too large quantities leads to digestive disturbances, and if carbohydrates are entirely abandoned, to acetonuria.

CHAPTER X

THE INFLUENCE OF THE INGESTION OF CARBOHYDRATE

PART II—THE RESPIRATORY METABOLISM

In a previous chapter (see p. 238) it has been stated that when Rubner gave cane-sugar to a dog and measured the metabolism during a period of twenty-four hours the heat production was raised by an increment amounting to about 5 per cent. of the calories ingested. This fact, which has been repeatedly confirmed, does not tell the whole story, because the absorption of the very soluble sugar takes place in the first few hours. Thus Magnus-Levy[1] noticed that after giving 155 grams of cane-sugar to a man there was a maximal increase in metabolism of 12 per cent., with a return to the basal level during the fifth hour after taking the food-stuff.

Johansson, Billström, and Heijl[2] have shown that if 50 to 200 grams of cane-sugar be given a fasting man, the carbon dioxid output increases from 22.6 grams per hour to about 30 grams per hour. The larger ingestion did not produce a higher elimination of carbon dioxid than does the smaller amount. This indicates the evenness with which sugar entering the blood-stream is utilized by the organism. If sugar be present in excess it may be stored as glycogen until it is needed by the cells. The rise in the carbon dioxid output was greater after fructose is ingested than after glucose is given. This was explained as due to the fact that fructose is less readily

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[1] Magnus-Levy: "Pflüger's Archiv," 1894, lv, 1.

[2] Johansson, Billström, and Heijl: "Skan. Archiv für Physiologie," 1904, xvi, 263.

retained in the liver as glycogen, and therefore reaches the tissues in a larger stream than does glucose under similar circumstances, and hence more completely replaces fat as the source of energy. In a later paper Johansson[1] explains that after ingesting 200 grams of glucose containing 740 calories, or one-quarter the man's energy requirement for a day, the rise in carbon dioxid output lasts for six hours and then falls to the fasting basis. This is an indication of the ready absorption and combustion of ingested glucose. If there has been prolonged fasting, ingested glucose may cause no rise in the carbon dioxid output in man on account of its conversion into glycogen. (See p. 273.)

Durig[2] gave 100 grams of glucose to a man and compared the metabolism with that obtained after giving 100 grams of fructose. In the latter case the heat production as measured by indirect calorimetry was 10 per cent. greater than in the former; the respiratory quotients were usually higher, being more frequently over unity, and therefore indicating a readier conversion of fructose into fat than was the case with glucose.

Du Bois[3] made calorimetric observations on men after giving 100 and 200 grams of glucose and noted the following increases above the basal metabolism:

PERCENTAGE INCREASE IN HEAT PRODUCTION AFTER GIVING GLUCOSE TO MAN

Hours After Food	1	2	3	4	5
Subject E. F. D. B., 100 grams glucose	3	11	9	6	
(R. Q.)	*(0.91)*	*(0.89)*	*(0.88)*	*(0.90)*	
Subject E. F. D. B., 200 grams glucose	....	13	17	8	7
(R. Q.)	....	*(0.95)*	*(0.93)*	*(0.95)*	*(1.00)*
Subject L. C. M., 200 grams glucose	....	24	16	16	
(R. Q.)	....	*(0.92)*	*(1.00)*	*(1.02)*	

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[1] Johansson: "Skan. Archiv für Physiologie," 1908, xxi, 30.

[2] Tögel, Brezina, and Durig: "Biochemische Zeitschrift," 1913, l, 298.

[3] Gephart and Du Bois: "Archives of Internal Medicine," 1915, xv, 835.

One hundred grams of glucose caused an average increase of 9 per cent. in the heat production and 200 grams one of 12.5 per cent. during three to six hours after their ingestion by a man of 75 kilograms in weight. Ingestion of 200 grams of glucose by a man of 60 kilograms weight caused an increase of 16 per cent. in the heat production. When the larger quantity was administered, the respiratory quotients indicated that the heat production was entirely at the expense of carbohydrate and protein.

The behavior of carbohydrate in many of its details may be best observed in experiments on animals.

Extensive calorimetric observations upon dogs have been carried out in the author's laboratory, and the following principles are believed to have been established:

After giving 50 grams of glucose to a dog Fisher and Wishart[1] found an increase in the percentage quantity of blood-sugar at the end of the first hour, and this was followed by a fall to the normal level. A similar phenomenon had been observed in man[2] after giving 150 grams of glucose; but in the dog it was further observed that when the sugar solution was given there was at first a considerable reduction in the quantity of urine eliminated. This appears from the following analysis:

QUANTITY OF URINE AS INFLUENCED BY FASTING AND BY WATER AND GLUCOSE INGESTION

Hour.	Fasting.	150 C.C. Water.	Glucose 50 Gm. in 150 C.C. Water.	Glucose 75 Gm. in 150 C.C. Water.
	C.C.	C.C.	C.C.	C.C.
1	7	28	7	6
2	2	27	7	6
3	4	28	12	7
4	3	17	100	19
5	..	..	66	89
6	..	..	22	

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[1] Fisher, G., and Wishart: "Journal of Biological Chemistry," 1912, xiii, 49.

[2] Gilbert and Baudouin: "Compt. rend. soc. biol.," 1908, lxv, 710.

These authors also found that the hour of the sudden increase in the quantity of urine eliminated coincided with the completion of the absorption of glucose from the gut, and with the last hour of increased metabolism as determined in Lusk's calorimeter experiments. These circumstances led them to investigate the hemoglobin content of the dog's blood. They discovered that although at the end of the first hour there was no alteration in this regard, yet at the end of the second hour, when between two-thirds and three-quarters of the ingested sugar had been absorbed from the intestine, the blood usually became more dilute, as shown by a fall in the percentage amount of hemoglobin. This indicates the continuance of a generous distribution of glucose molecules to the tissues by means of an increase in the volume of the nourishing fluid.

With the cessation of absorption and the return of the blood to its normal volume the metabolism falls to its basal level, the respiratory quotient frequently falls, and there is every indication of a regulation of the carbohydrate supply to the tissues by the liver so that fat and carbohydrate are oxidized together. Only when this food supply is supplemented by carbohydrate from the gut does the metabolism rise. Such an increase may, therefore, be properly termed the "metabolism of plethora." It was furthermore shown that during the period of absorption there was little retention of glycogen by the liver—the absorbed glucose apparently passed freely into the tissues. The largest glycogen content of the liver was found during the last hour of absorption, the last of high metabolism, and the hour characterized by passage of a large volume of urinary water. This was the hour when the liver assumed the duty of arbiter over the carbohydrate supply to the cells.

The calorimetric and respiratory experiments which established these interrelations are portrayed in the accompanying chart (Fig. 20).

The experiments showed that the height of the metabolism was about the same whether 50 or 75 grams of glucose were given, only in the latter case the effect was more prolonged. This is in accord with Rubner's idea of "self-regulation," and also accords with the fact that the fermentative activity of living yeast cells is independent of the concentration of the sugar solution in which they live.[1]

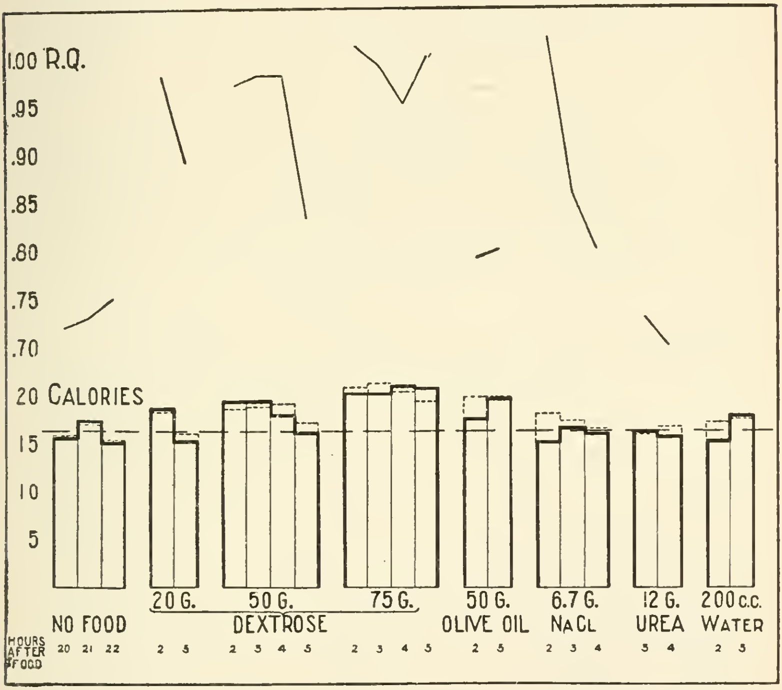

Fig. 20.—Illustrating the effect of the ingestion of glucose and fat and of water, urea, and salt solutions on the metabolism. Solid lines—metabolism in calories as calculated. Broken lines—metabolism in calories as found.

What is the cause of the increased metabolism after the ingestion of glucose? In Fig. 20 it appears that the administration of 150 c.c. of water, either alone or containing 6.7 grams of sodium chlorid or 17 grams of urea, has no effect

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[1] Rubner: "Sitzungsberichte der k. preussischen Akademie der Wissenschaften," 1913, viii, 232.

upon the heat production. Therefore neither osmotic exchanges nor increased kidney function, nor intestinal absorption can play any part in the increased heat production.

These experiments led to further investigations[1] to inquire into the cause of the rise in heat production after glucose ingestion. To this end various carbohydrates were given to the same dog in quantities of 50 grams. The fact that fructose exerted a more powerful influence on metabolism than glucose was confirmed. It was also shown that galactose oxidized with much greater difficulty in the dog than the other two monosaccharids, as evidenced by a lower metabolism and a lower respiratory quotient, and that lactose was not oxidized at all, and therefore caused no increase in the heat production. This latter fact must have been due to the absence of lactase from the intestine. These relations are shown in the following table:

INFLUENCE OF 50 GRAMS OF VARIOUS CARBOHYDRATES UPON THE METABOLISM OF THE DOG

Experiment No.	Sugar 50 Gm.	Average R. Q.	2, 3, and 4 Hours.
			Percentage of Increase Over Indirect Basal Metabolism.
34, 36	Glucose	1.00	30
64, 66, 67	Fructose	1.02	37
60, 58	Sucrose	1.02	34
67	Galactose	0.93	22
62	Lactose	0.90	3

Weinland[2] has shown that galactose does not form glycogen as readily as do glucose and fructose. From these facts it is most probable that galactose does not as readily dissociate into easily oxidizable molecules as do glucose and fructose.

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[1] Lusk: "Journal of Biological Chemistry," 1915, xx, 555.
[2] Weinland: "Zeitschrift für Biologie," 1899, xxxviii, 16 and 607.

By similar reasoning one may explain the difference in behavior between glucose and fructose. Glucose molecules require simple dehydration for conversion into glycogen and may in that fashion be removed from the tissue fluids. Fructose cannot be thus removed. It must first undergo chemical change, very likely by fragmentation into methyl-glyoxal with its three-carbon chain (formula on p. 265) before it can be synthesized into glycogen. These molecules being then in greater mass than similar molecules derived from ingested glucose would have been, it is easy to conceive that a higher metabolism would result on account of the greater plethora of oxidizable particles. F. G. Benedict[1] states that the cause of the specific dynamic action of carbohydrates is the formation of acids, which act as stimuli. In support of this he cites an experiment by Benedict and Joslin,[2] in which an increase of 30 per cent. in the heat production of a diabetic woman took place after the ingestion of 100 grams of fructose, notwithstanding the fact that the respiratory quotient before and after administration of the sugar was 0.69, indicating that none of the fructose was oxidized. Since fructose is transformed into glucose in the diabetic organism, Benedict interpreted this experiment as indicating the formation of acid intermediary products which stimulated metabolism.

Lusk has proved that when 12.5 grams of glycocoll, which are convertible into 10 grams of glucose, are given to a phlorhizinized dog, the heat production is largely increased (see p. 244). Not so, however, with fructose. When 10 grams of fructose, which are convertible into 10 grams of glucose, are given to a phlorhizinized dog there is no increase whatever in metabolism. The chemical intermediates between fructose and glucose are without stimulating influence. This appears in the following experiment:

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[1] Benedict, F. G.: "Transactions of the XVth International Congress of Hygiene," 1912, ii, 394.

[2] Benedict and Joslin: "Metabolism in Severe Diabetes," 1912, p. 69.

THE INFLUENCE OF FRUCTOSE IN PHLORHIZIN GLYCOSURIA

Exp. No.	Conditions.	Hours.	Urinary D : N.	R. Q.	Non-protein R. Q.	Calories.	
						Protein.	Total Indirect.
81	Eighth day fasting and phlorhizin.	1	4.22	0.719	0.75	7.04	26.57
		2	4.22	0.711	0.74	7.04	27.62
	Average.	. .	. .	0.715	. .	. .	27.10
	Same after fructose 10 gm.	2	7.31	0.697	0.72	6.08	25.80
		3	7.31	0.697	0.72	6.08	25.80
		4	7.31	0.680	0.70	0.08	24.78
	Average.	. .	. .	0.692	. .	. .	25.46

From the fact that the ingestion by a phlorhizinized dog of alanin, which certainly yields lactic or pyruvic acids in metabolism, causes a considerable rise in the heat production, (see p. 244), one may conclude that such acids are not intermediary metabolites in the reaction which converts fructose into glucose.

It may be added that if much acid be produced in carbohydrate metabolism, one would expect to find an increased quantity of ammonia in the urine during the oxidation of carbohydrate, just as ammonia elimination increases when lactic acid is formed in phosphorus-poisoning, but such an increase is not observed.[1] Furthermore, if there were a considerable production of acid as a result of carbohydrate oxidation one would expect to find a fall in the quantity of carbon dioxid in the blood, such as occurs after giving meat, whereas unpublished experiments done by Dr. A. L. Meyer in the author's laboratory show that this is not the case—the quantity of carbon dioxid remains unchanged.

It is interesting to note that Freise[2] found that when a surviving dog's liver is perfused with blood it yields 55 to 192

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[1] Murlin and Lusk: "Journal of Biological Chemistry," 1915, xxii, 15.

[2] Freise: "Biochemische Zeitschrift," 1913, liv, 474.

milligrams of carbon dioxid per minute per kilogram of substance. Addition of glucose, pyruvic acid, lactic acid, or glyceric acid increases the carbon dioxid 50 per cent., whereas galactose, glyoxylic, glycollic, and acetic acids were without influence.

It is, of course, known that the end-product of sugar metabolism, carbonic acid, is a stimulus to the respiratory center; but the end-product cannot be the cause of its own increased production for the following reasons: If methylglyoxal be an intermediate it may pass, on the one hand, back into glucose, and, on the other, forward into acetaldehyd with the elimination of carbon dioxid.

$$C_6H_{12}O_6—2H_2O \longrightarrow CH_3.CO.CHO + H_2O \longrightarrow CH_3.CHO + CO_2 + H_2$$

The reader is referred to p. 268, on which is described how by this process the transformation of carbohydrate into fat may occur. Now if, under these conditions, there is a great stimulation of metabolism, one would expect to find after giving an excess of carbohydrate that the heat production would be proportional to the amount of fat synthesized in the organism. This is emphatically not true. Neither the extra volume of carbon dioxid produced, which carries the respiratory quotient above unity, nor the extra metabolites involved in the reaction are effective in materially increasing the heat production (see p. 308).

It would seem that the real cause of the increased heat production after carbohydrate ingestion lay in the plethora of acetaldehyd molecules, which the cells, within the limits of the definite upper level imposed by self-regulation, were capable of utilizing. Above this level the acetaldehyd molecules are convertible into fat with little loss in the original energy content of the sugar from which they arise.

The subject may be approached from still another standpoint, combining the influence of carbohydrate with that of amino-acids and other food-stuffs. The following observations have been made by the author.[1] When 50 grams of glucose were administered to a dog the heat production increased 30 per cent.; with 70 grams, the increase was 35 per cent. Twenty grams of glycocoll increased it 36 per cent., and the same amount of alanin, 32 per cent. Combined, 50 grams of glucose and 20 grams of glycocoll are the glucose equivalent of 66 grams, and yet when they were given together the metabolism increased 56 per cent., an increase greater than 66 grams of glucose could have induced. Glucose and alanin in similar quantities are a glucose equivalent of 70 grams and caused an increase in heat production of 53 per cent. It is obvious that an increase in the quantity of glucose when this is given in large amounts scarcely affects metabolism; but that the chemical stimulus of amino-acids acting in conjunction with a plentiful supply of glucose results in a rise in heat production which is nearly the sum of the two individual influences acting separately. This points to a distinct difference between the cause of the specific dynamic action of glucose and that of alanin, which latter is convertible into lactic acid and eventually into glucose.

Lactic acid from alanin or glycollic acid from glycocoll may therefore raise the level of cell activity through direct stimulation; and if fragments of glucose metabolism be present in quantity, these may enter as increased fuel to produce yet higher metabolism in the cells than the oxyacids would alone induce.

Also, when alcohol is given with glucose the metabolism rises above the level it would have attained had glucose been administered alone. The respiratory quotient falls, the cells oxidize both alcohol and the fragments of glucose metabolism, and produce almost as much extra heat as the sum of the quantities of heat which each material would have induced alone.

These experiments were extended by Murlin and Lusk,[2]

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[1] Lusk: *Loc. cit.*

[2] Murlin and Lusk: "Journal of Biological Chemistry," 1915, xxii, 15.

so that the influence of glycocoll, glucose, and fat when ingested severally and together could be analyzed.

It was found that if glucose be ingested at the time of the highest fat metabolism, the heat production undergoes a second increase to the same extent which glucose alone would have increased metabolism. At this level of higher metabolism the respiratory quotient is 0.93 or 0.94, instead of unity, which it would have been if glucose had been given alone, hence glucose and fat were being oxidized together. The urinary ammonia fell following the ingestion of glucose four hours after fat ingestion, and this was true in spite of the combined oxidation of fat and carbohydrate. This does not suggest the presence of acid formation as the cause of the high metabolism.

When glucose and glycocoll are given together so that their molecules enter the circulation at the time of the height of fat absorption, the increase in metabolism is very nearly equal to the sum of the increases which each of the three materials would have induced alone.

The following table and accompanying chart (Fig. 21, p. 300) show these relations:

THE EFFECT OF GLYCOCOLL, GLUCOSE, AND FAT, SEVERALLY AND TOGETHER

Dog XIV. Second Series.

Experiment Nos.		R. Q.	Cal. per Hour.	No. of Hours.	Increase Over Normal.	
					Cal.	Pr. Ct.
15, 17, 21	Basal	0.86	22.7	3		
20	Fat, 75 grams	0.80	26.6	4*	3.9	17
18	Glycocoll, 20 grams	0.90	27.6	2	4.9	25
16, 19	Glucose, 70 grams	1.02	29.6	2	6.9	30
23	Glucose, 50 grams + glycocoll, 20 grams	1.03	33.5	2	10.8	48
24	Glucose, 50 grams + glycocoll, 20 grams, given four hours after fat, 75 grams	1.02	37.3	2	14.6	64

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* Hours 6, 7, 8, 9 after fat ingestion.

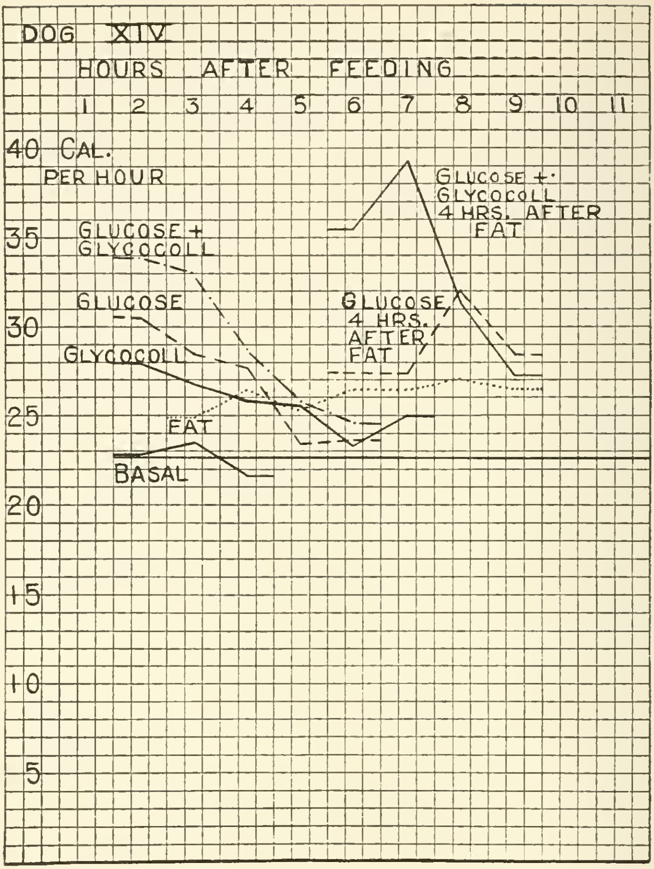

Fig. 21.—The effect of fat, of glycocoll, of glucose, of glucose + glycocoll, and of glucose + glycocoll + fat upon the heat production. (The "glucose four hours after fat" curve is atypical, is not similar to other experiments, and probably denotes a slow emptying of the stomach).

From the data obtained with this dog the following computation may be made, which shows that the sum of the individual increases of heat production caused by each substance is only a little more than the total heat production when all the substances are given together:

	Calories.	Per Cent.
Glycocoll, 20 grams	4.9	25
Glucose, 70 grams	6.9	30
Fat, 75 grams	3.9	17
Sum of all	15.7	72
Glycocoll, 20 gm. + glucose, 50 gm., 4 hrs. after fat, 75 gm	14.6	64

A Theory of Metabolism

Rubner[1] conceived that the living cell had essentially two nutritive affinities—one for fat, the other for carbohydrate. When, as in diabetes, the affinity for carbohydrate was rendered inactive, fat alone oxidized for the maintenance of the body. Rubner's theory of metabolism is given on p. 239.

The more intimate knowledge derived from the study of the action of intermediary metabolites during short periods of time compels another viewpoint. In presenting the following interpretation, the writer is keenly aware of the transitory character of all theories.[2]

In each mammal there is a *basal metabolism*. This corresponds with the minimal heat production eighteen hours after taking a mixed diet. Under these circumstances the cells are nourished by a food supply of fat and of carbohydrate, the latter supply being regulated by the liver. The basal metabolism may be acted on by food in the following ways:

(1) *Amino-acid stimulation*, in which some oxy- or keto-acids derived from protein metabolism stimulate the cells to a higher level of oxidative activity.

(2) *Fat plethora*, in which an influx of fat from the gut increases the heat production at the expense of fat itself. When fat is oxidized two carbon atoms are broken from the

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[1] Rubner: "Archiv. für Hygiene," 1908, lxvi, 15.

[2] During the discussion which followed the presentation of papers on the subject of the specific dynamic action of the food-stuffs at the International Congress of Hygiene and Demography held at Washington in 1912, Professor Rubner said: "Ich freue mich dass die Frage der 'specific dynamic action' durch neue Untersuchungen weiter geführt worden ist. Die Erklärungen der Tatsachen wechseln mit der Zeit: das ist die Geschichte der Wissenschaft. Ich freue mich constatieren zu können, dass meine alten Untersuchungen nun endlich bestätigt worden sind."

chain together. What form this cleavage takes is not known; it is usually pictured as productive of acetic acid. If palmitic acid broke up by successive oxidations into acetic acid radicles, one could write the following reaction:

$$\begin{array}{ccccc} C_{16}H_{32}O_2 & + & 14O & = & 8C_2H_4O_2 \\ \text{Palmitic acid.} & & & & \text{Acetic acid.} \\ \text{1 gram} & & & = & \text{1.348 grams} \\ \text{9353 calories} & & & = & \text{4706 calories} \end{array}$$

Such a reaction involves 50 per cent. loss of heat. Perhaps the energy imparted to the cell in fat metabolism is derived from a twofold source—acetic acid and the oxidation at the β-carbon atom of the fatty acid; or perhaps a substance more highly explosive than acetic acid is set free as the result of β-oxidation. In any event one may conceive of the oxidation of fat as being in the nature of successive ultra-micro explosions, which act as power for the machinery of the cells.

(3) *Carbohydrate plethora*, in which an influx of carbohydrate from the intestine increases the heat production. When these enter the circulation alone they are oxidized to the exclusion of fat. It appears certain that the intermediary metabolites of glucose and fructose are far more readily oxidizable than fat, and on this account, when they are present, they satisfy the energy requirements of the cell and the fat is not attacked. If glucose breaks up into methyl-glyoxal and this into acetaldehyd and formic acid, the reaction would be as follows:

$$\begin{array}{lcccccccc} C_6H_{12}O_6 - 2H_2O & \longrightarrow & 2C_3H_4O_2 & + & 2H_2O & \longrightarrow & 2CH_3.CHO & + & 2HCOOH \\ \text{Glucose.} & & \text{Methyl-glyoxal.} & & & & \text{Acetaldehyd.}^1 & & \\ \text{1 gram} & & & & & & \text{0.4889 gram} & & \\ \text{3.762 calories} & & & & & & \text{3.098 calories} & & \end{array}$$

According to this computation, and assuming that hydrolytic reactions are accomplished without thermal changes, 79 per cent. of the energy liberated in carbohydrate metabolism

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[1] If the hydrogen in formic acid were oxidized to water ($HCOOH \longrightarrow CO_2 + H_2$, $H_2 + O = H_2O$) the heat evolved would be 0.755 calorie. The heat of combustion of formic acid is unknown.

would be derived from acetaldehyd and 21 per cent. from formic acid.

There is no indication of a physiologic separation of these two varieties of energy. It happens frequently that with the cessation of glucose absorption the respiratory quotient remains at 1.00, indicating that carbohydrate is still the essential food, and yet the metabolism has fallen to the basal level. One must, therefore, conclude that the metabolism increases only in the presence of a *plethora* of dissociated fragments of sugar. The metabolism may rise to a certain height which is not transcended, and an excess of metabolites above this level may be converted into fat (see p. 308) with scarcely any energy loss.

(4) *Carbohydrate and Fat Plethora.*—Here there is a summation of effect. It seems as though that part of the cell mechanism which is susceptible to fat metabolism *when fat is present in excess* is not inhibited from metabolizing such surplus fat even in the presence of carbohydrate.

(5) *Amino-acid Stimulation and Carbohydrate and Fat Plethora.*—Simultaneous ingestion of an amino-acid and carbohydrate acts in such a manner as to suggest that the increase in metabolism due to carbohydrate plethora is essentially independent of that due to the chemical stimulus of amino-acids. Also when an amino-acid is given together with glucose at the height of fat metabolism (four hours after fat ingestion) the increase in heat production is nearly one amounting to a summation of the three influences.

One may, therefore, conclude that the influence of food upon the quiet resting cell under these circumstances is upon three independent mechanisms within the cell:

(*a*) A mechanism which is receptive to a chemical stimulus derived from the metabolism of such amino-acids as glycocoll and alanin.

(*b*) A mechanism of carbohydrate plethora which allows the metabolism of carbohydrate up to the limits imposed by "self-regulation."

(*c*) A mechanism capable of receiving power from that quota of fat which when in excess increases the heat production of the cell.

THE CONVERSION OF CARBOHYDRATE INTO FAT

Voit, when he wrote his "Physiologie des gesammt Stoffwechsels und der Ernährung," in 1881, was unable to give definite proofs of the conversion of carbohydrate into fat in the organism, although such conversion was popularly believed to take place. Definite proof of the conversion of carbohydrates into fat was afforded by Meissl and Strohmer,[1] who gave a pig, weighing 140 kilos, 2 kilograms of rice containing 1592 grams of starch daily for seven days, and collected the carbon and nitrogen of the excreta by means of a Pettenkofer-Voit apparatus during two days of the period. The average results per day were as follows:

	Carbon, Grams.	Nitrogen, Grams.
Ingested in food	765.37	18.67
Excreted	476.15	12.59
Balance retained in the body	289.22	6.08

The nitrogen retained represented 38 grams of protein containing 20.1 grams of carbon; 269.12 grams of retained carbon were therefore available for glycogen or fat construction. Since the amount of carbon retained exceeded the possible glycogen formation, fat must, therefore, have been added to the body. Had all the carbon retained been converted into fat it would represent a production of 343.9 grams of fat. Of this only 33.6 grams of fat could have arisen from the protein metabolism of the period. Hence it is possible that 310.3 grams of fat may have originated from 1592 grams of starch ingested, which indicates a conversion of 19.5 per cent. of the starch given into fat.

Similar experiments were made with geese by E. Voit and

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[1] Meissl and Strohmer: "Sitzungsberichte der k. Akad. d. Wissenschaften," 1883, lxxxviii, III Abtheilung.

C. Lehmann.[1] The geese were starved four and a half days and were then fed with rice.

One of these respiration experiments which lasted thirteen days has been published,[2] and is as follows:

	NITROGEN.	CARBON.
In the 2609 grams of rice	41.47	1159.7
In the excreta—		
Urine and feces	45.39	134.8
Respiration	.....	657.8
Total	45.39	792.6
Change in the body	−3.92	+367.1

At the commencement of the experiment the animal weighed 4 kilograms. There was no protein retention, but 31 per cent. of the carbon ingested was not eliminated. The protein metabolism could not yield nearly enough carbon to account for that retained. As the rice contained but 0.51 per cent. of ether extract, the retained carbon could not have been administered in the form of fat. If 367.3 grams of carbon had been retained in the form of glycogen this would have aggregated 851 grams, or 20 per cent. of the whole goose, or the starch content of a potato. This is a manifest impossibility, since E. Voit[3] found only 2.2 per cent. of glycogen in a goose which had been largely fed on rice. Since the carbon retained could not have been stored as glycogen, the only alternative remaining is to assume its retention as fat.

Rubner about the same time showed the same principles to be true in the case of the dog.

It is evident, then, that pigs, geese, and dogs can convert carbohydrates into fat. The fattening of cattle may be similarly accomplished.

The ability to convert carbohydrate into fat probably exists throughout the animal kingdom. Thus Weinland[4] has expressed from living ascaris ferments which convert glycogen

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[1] Voit: "Sitzungsberichte der kgl. bayr. Akad. d. Wissenschaft," 1885, p. 288.

[2] Lehmann and E. Voit: "Zeitschrift für Biologie," 1901, xlii, 644.

[3] E. Voit: *Ibid.*, 1889, xxv, 543.

[4] Weinland: *Ibid.*, 1901, xlii, 55; 1902, xliii, 86; 1904, xlv, 113.

into glucose and then into valerianic and possibly caproic acids—0.8 gram of dextrose yields 0.3 gram of valerianic acid.

This is suggestive of a wide-spread biologic capability.

When carbohydrates are converted into fat in the organism the respiratory quotient ($\frac{\text{Volume } CO_2}{\text{Volume } O_2}$, see p. 57) may rise very considerably above unity. This is for the reason that an oxygen-rich substance like glucose is being converted into substance which is poor in oxygen. Hence the volume of expired carbon dioxid may be greater than the volume of inspired oxygen. Max Bleibtreu[1] found that the respiratory quotient of a goose which had been stuffed with grain was 1.33, whereas the same goose when fasting showed a normal quotient for that condition of 0.728. Pembrey[2] describes how marmots previous to the winter hibernation instinctively devour large quantities of carbohydrate food, and how the respiratory quotient may rise even as high as 1.39. This indicates a fat production for use during the winter.

Grafe[3] gave to a fasting dog three times his daily caloric requirement of energy in the form of carbohydrate, and noted an increase of 33 per cent. in the heat production and a maximal non-protein respiratory quotient of 1.31. A discussion of the intermediary chemical reactions involved in this process has already been given (see p. 268). Written in their simplest formulæ the production of butyric or of palmitic acids from glucose would read:

$$C_6H_{12}O_6 + O_2 = C_4H_8O_2 + 2CO_2 + 2H_2O$$

$$4C_6H_{12}O + O_2 = C_{16}H_{32}O_2 + 8CO_2 + 8H_2O$$

One may accept Bleibtreu's formula as the simplest expression of the conversion of carbohydrate into fat, as follows:

270.6 gm. glucose = 100 gm. fat + 115.45 gm. CO_2 + 54.6 gm. H_2O
997.2 calories = 950.0 calories.

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[1] Bleibtreu: "Pflüger's Archiv," 1901, lxxxv, 345.

[2] Pembrey: "Journal of Physiology," 1901, xxvii, 407.

[3] Grafe: "Deutsch. Archiv für klin. Med.," 1914, cxiii, 1.

The reaction is evidently exothermic, 4.7 per cent. of the heat being liberated. If the heat evolved be measured on the basis of the extra carbon dioxid production, 1 liter of such carbon dioxid would have a value of 0.8 calorie, or less than one-sixth the caloric equivalent of a liter of carbon dioxid obtained from the oxidation of glucose in the ordinary manner.

On the basis of this the heat production of a dog after giving 70 grams of glucose was calculated in experiments performed by Lusk.[1] The results of two of the three experiments are presented in the accompanying table:

DOG III. METABOLISM AFTER GIVING 70 GRAMS OF GLUCOSE IN 210 C.C. OF WATER AT 38°

	Experiment 88.				Experiment 91.			
Hours.	Non-protein R. Q.	Indirect Uncorrected.	Indirect Corrected.	Direct.	Non-protein R. Q.	Indirect Uncorrected.	Indirect Corrected.	Direct.
		Calories.	Calories.	Calories.		Calories.	Calories.	Calories.
2	1.03	25.24	25.34	26.12	1.08	24.52	24.78	25.31
3	1.11	24.89	25.26	25.83	1.14	24.91	25.38	25.63
4	1.12	24.82	25.21	24.86	1.16	24.98	25.49	25.12
		74.95	75.81	76.81		74.41	75.65	76.06

That the method of calculation of indirect calorimetry in the presence of respiratory quotients above unity is correct may be deduced from these experiments. The "uncorrected" heat values represent calculations based on the oxygen absorption alone, while the "corrected" values are those in which the quantity of CO_2 eliminated in excess of a non-protein respiratory quotient of unity is given a value of 0.803 calorie per liter.

It is evident that after a large ingestion of glucose direct and indirect calorimetry agree closely if the heat value of the carbon dioxid which is evolved in the intermediary transformation of carbohydrate into fat be taken into consideration.

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[1] Lusk: *Loc. cit.*

During the first three hours of Experiments 88, 90, and 91 the calculated heat production was 75.81, 75.30, and 75.64, while the CO_2 excretion in excess of a non-protein respiratory quotient of 1.00 was 1.07, 0.80, and 1.73 liters; it is, therefore, apparent that the intensity of metabolism is not related to the height of the respiratory quotient. The transformation of carbohydrate into fat takes place with the liberation of very little energy, and the height of the total metabolism is scarcely affected by the process.

CHAPTER XI

THE INFLUENCE OF MECHANICAL WORK ON METABOLISM

In the account of metabolism during starvation a short description has already been given of the influence of mechanical work on protein metabolism, of the influence of posture on general metabolism, and of the relation of the amount of metabolism to the diurnal variations of human temperature.

The source of mechanical work must be from metabolism, for mechanical energy cannot be derived from nothing. The necessary energy might be obtained in one of two ways, either at the expense of a proportionate reduction in the quantity of heat liberated by the resting organism, or by an increase in the amount of the metabolism. In the former case work would diminish the heat production and might cool the tissues, which is not observed to take place. If work were done at the expense of increased metabolism, and if this increase were completely converted into mechanical effect, then the heat production in the organism might remain the same as in the resting state. If, however, the result of mechanical effort be a stimulation of metabolism to the extent of not only enabling the body to do work but also causing it to produce more heat than when at rest, then the tendency of the tissues must be to grow warmer, perhaps with a resulting outbreak of sweat to reduce the body temperature through physical regulation. The last named is the actual process.

Lavoisier's discovery that the absorption of oxygen is increased during mechanical exercise firmly established the fact of a higher metabolism under these conditions.

The first experiments in which the effect of work upon the total metabolism was demonstrated were made upon a man by Pettenkofer and Voit.[1] A man turned an ergostatic wheel 7500 revolutions on each working day for a period of nine hours, which afforded sufficient exercise to cause great fatigue at the end of the day. The experiments were made both during hunger and when the man was ingesting a medium mixed diet. The food supplied in the mixed diet contained:

	Grams.	Calories.
Protein	121.7	506
Fat	117.	1088
Carbohydrates	352.	1443
Total		3037

The metabolism of this man, a strong workman, weighing 70 kilograms, at rest and at work, starving or on the medium mixed diet as given above, is presented in the following table:[2]

EFFECT OF MECHANICAL WORK ON METABOLISM IN MAN

	Grams Metabolized.			Cal. of Metabolism.	Cal. above Fasting Quantity.	Experiment No. of Pettenkofer and Voit.
	Protein.	Fat.	Carbohydrates.			
Starvation—Rest	70.8	222	...	2374	....	I
" —Rest	68.7	208	...	2231	....	III
" —Work	66.1	387	...	3882	1582	IV
Mixed diet—Rest	121.7	73	352	2638	336	V
" —Rest	118.7	93	352	2714	412	VI
" —Rest	125.0	84	352	2750	458	VII
" —Work	121.7	208	352	3856	1554	VIII
" —Work	122.0	152	352	3378	1076	IX

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[1] Pettenkofer and Voit: "Zeitschrift für Biologie," 1866, ii, 537.

[2] I have multiplied the nitrogen of the ingesta and excreta by 6.25 to obtain the quantity of the protein given and metabolized. The ratio N : C = 1 : 3.28 in protein has been employed. The dry starch has been calculated as containing 44.2 per cent. and the fat as containing 76.5 per cent. of carbon, which were the figures used by Pettenkofer and Voit. Rubner's standard calorimetric values have been used. (See Introductory Chapter.)

From these early experiments it was evident that mechanical work did not increase protein metabolism even in starvation, but that the power to do work might readily be supplied by the increased metabolism of fat.

In the earlier editions of this book (1906 and 1909), the question was asked whether energy evoked by the specific dynamic. action of the food-stuffs could be utilized in the production of mechanical work.

The following experiments by Rubner[1] show beautifully that *there is a summation of function as regards the extra heat production due to the specific dynamic action of protein and the extra heat production incident to mechanical work:*

THE INFLUENCE OF DIET AND MECHANICAL WORK UPON THE METABOLISM OF A MAN 61–63 KG. IN WEIGHT

DIET AND CONDITIONS.	CALORIES PRODUCED.			HEAT LOSS.		
	Twenty-four Hours.	Increase.	Increase Due to Work.	Evap. H_2O.	Rad. and Cond.	Work.
	Calories.	Per Cent.	Calories.	Calories.	Calories.	Calories.
No food, rest..........	1976	....	....	380	1596	
Cane-sugar 600 gms. + H_2O 3000 gms., rest..	2023	+ 2.4	....	529	1494	
Same + work (100,000 kg.)................	2868	+45.2	845	907	1727	234
Protein, large amount of meat, rest...........	2515	+27.2	....	614	1901	
Protein, same diet, + work (100,000 kg.)..	3370	+70.5	855	1235	1901	234

Rubner observed that mechanical work was performed with greater ease when cane-sugar was the basis of the diet than when protein was given. The temperature of the chamber in which the experiments were performed was about 20° and the humidity was about 40 per cent. Rubner calls especial attention to the fact that when cane-sugar was given the increased heat produced by the body was lost, partly by the increased evaporation of water (62 per cent. of the increased

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[1] Rubner: "Sitzungsberichte der preussischen Akademie der Wissenschaften," 1910, xvi, 316.

heat production) and partly by an increase in radiation and conduction from the skin (38 per cent. of the increased heat production), whereas after meat had been given the elimination of the entire extra heat production due to work was thrown upon the activity of the sweat-glands. A high protein dietary is therefore contraindicated in athletic contests, especially when the weather is hot and humid.

The 100,000 kilogrammeters of work described above were produced by the action of the arms upon an ergostat. Since this quantity of work is the mechanical equivalent of 234 kilo-calories, and since 850 extra calories of metabolism were invoked in its accomplishment, it is evident that the mechanical efficiency of the human engine under these circumstances was $\frac{234}{850}$, or 27.5 per cent.

Benedict and Murschhauser[1] confirm the summation of energy increase from food and work in the case of men walking in a horizontal direction.

Recent investigations in my laboratory, however, indicate that a small dog, accomplishing a given amount of mechanical work, shows nearly the same heat production without food as after the ingestion of 70 grams of glucose. This is an important fact.

Rubner[2] shows that a man of 70 kilograms weight, developing mechanical energy to the extent of 15,000 kilogrammeters per hour, produces practically the same quantity of carbon dioxid, no matter what the temperature of his environment may be. The results of the experiment are as follows:

Temperature of the Air.	Percentage Moisture in the Air.	Carbon Dioxid per Hour in Grams.	Water Excreted per Hour in Grams.
7.4°	81	84.0	58.0
12.7°	84	78.5	70.8
16.7°	59	97.0	138.1
17.5°	87	84.5	90.4
18.8°	83	81.2	112.8
25.0°	47	78.7	230.0

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[1] Benedict, F. G., and Murschhauser: "Energy Transformations During Horizontal Walking," Carnegie Institution Publication 231, 1915, p. 91.

[2] Rubner: Von Leyden's Handbuch, "Die Ernährungstherapie," 1903, Bd. i, p. 74.

This person while at rest and at a temperature of 21.1° excreted 33.6 grams of carbon dioxid and 42 grams of water.

It is clear that during work the metabolism is independent of surrounding temperature or climatic conditions. In other words, *during mechanical work the influence of the "chemical regulation" of body temperature may be eliminated* (see p. 134). The extra heat production in doing mechanical work is utilized instead of the production of heat which is excited reflexly through cold. These results were forecast by Voit.[1]

Generally speaking, neither clothing nor temperature affects the amount of the metabolism during exercise. They influence only the quantity of water eliminated in the perspiration, in the effort of the body to maintain its normal temperature through physical regulation. It is evident from Rubner's details of the water excretion that at a low temperature the extra heat production during mechanical exercise is lost by radiation and conduction. Rubner explains that the slight increase in the excretion of water above that lost while at rest is due to its increased evaporation through increased respiratory activity. At a higher temperature conduction and radiation become insufficient to cool the body, and a large proportion of the loss of heat takes place at the expense of the evaporation of sweat.

In hot, moist climates, however, the cooling of the body through the evaporation of moisture becomes difficult, and this is especially pronounced in the case of fat people (p. 147), who with difficulty discharge the heat produced within them. Broden and Wolpert[2] show the effect of the action of temperature and humidity on the metabolism of a fat man, weighing 101 kilograms, who executed the same amount of mechanical work under various conditions of experimentation. The work was light, being 5375 kilogrammeters per hour. The results were as follows:

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[1] Voit: "Zeitschrift für Biologie," 1878, xiv, 152.

[2] Broden and Wolpert: "Archiv für Hygiene," 1901, xxxix, 298.

EFFECT OF WORK, TEMPERATURE, AND HUMIDITY ON THE METABOLISM OF A FAT INDIVIDUAL

Temperature.	Grams per Hour.			
	Dry Air.		Humid Air.	
	CO_2 in Grams per Hour.	H_2O in Grams per Hour.	CO_2 in Grams per Hour.	H_2O in Grams per Hour.
20°	47.8	. .	46.4	
28–30°	47.3	. .	48.0	
36–37°	50.3	319+38 gm. sweat.	60.7	269 + 266 gm. sweat.

This individual was the same already mentioned (p. 147), and the explanation given there is equally applicable here. In a dry climate the same amount of mechanical work may be accomplished by a fat person at both 20° and 30° without changing the metabolism. At a temperature of 37° the metabolism rises, for the cooling power of the evaporating sweat does not seem sufficient to act through the dense covering of fat. This action is intensified in moist air, where the evaporation of water is hindered. Under these latter conditions the small amount of work was accomplished only at the expense of great discomfort and profuse perspiration.

The obese, therefore, work under great disadvantage in a hot, and especially in a hot and moist, climate. The profuse perspiration explains their desire for water to drink.

In the early experiments of Pettenkofer and Voit, already cited, it was shown that work did not raise the protein metabolism even in starvation, and that the source of the power appeared to be the increased combustion of the non-nitrogenous fat.

In other experiments a slight rise in the nitrogen metabolism, continuing into the day following work, has been noted. The protein metabolism, however, is not sufficient to yield the energy necessary for a hard day's work. In the well-known experiments of Fick and Wislicenus[1] the authors climbed the Faulhorn, in Switzerland, a mountain 1956 meters high. The product of their weight into the height to which they raised themselves gave them a close approximation to the amount of the work done. The experimenters took their last nitrogenous food seventeen hours before starting on their walk. They climbed for six hours and collected the urine of this period and that of seven hours thereafter. Their results were as follows:

	Urinary N of 13 Hours, Grams.	Dynamic Value of N in Kgm.	Body Weight, Kgm.	Height of Faulhorn.	Work in Kgm.
Fick	5.74	63,378	66	1956 meters.	129,096
Wislicenus	5.54	61,280	76	1956 "	148,656

The work accomplished represents three times the energy liberated from the protein metabolism of the time. The output of energy as measured above was not all the increase in the amount of mechanical energy during the period, for the heart and respiratory muscles acted with greater force, and energy was expended by swinging the arms and by friction on the road.

The fact observed by Pettenkofer and Voit that protein metabolism may not be appreciably affected during mechanical work has been abundantly confirmed by Krummacher.[2] A porter, weighing 79 kilograms, was given a diet containing 3700 calories, 14.28 grams of protein nitrogen, and a large amount of carbohydrate. The man turned a dynamometer and produced 402,000 kilogrammeters of work. The slight increase in protein metabolism could have yielded but 3 per cent. of the energy required for the work. Krummacher states that protein metabolism may increase during work only when the non-nitrogenous fat and carbohydrates become

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[1] Fick and Wislicenus: "Myothermische Untersuchungen," 1889.

[2] Krummacher: "Zeitschrift für Biologie," 1896, xxxiii, 108.

less available in metabolism. We have already seen that protein metabolism rises in the absence of carbohydrates. It may be that with the exhaustion of carbohydrates during exercise a period ensues when the loss of their influence leads to an increased protein destruction. The larger the quantity of carbohydrates given, the less marked would be this influence. It is interesting in this connection that soldiers when starting on a march may have a high respiratory quotient (indicating the combustion of carbohydrates), which falls at the end of the march (fat combustion) and which may remain lower than at first, even on a day following the march.[1] The fact that mechanical work may be accomplished at the expense of an increased combustion of fat and carbohydrates should not cause one to forget that protein *may* become the sole source of energy in the body. It has already been shown that a fasting animal, after burning all his fat, may maintain his life on protein alone (see p. 101), and that Pflüger kept a dog in active condition on meat alone. As protein may yield 58 per cent. of sugar this substance may still be the principal source of energy.

The following experiment not only indicates the fully proved point that muscular work does not increase protein metabolism, but it also shows that *the character of the protein metabolism is unchanged by muscular activity.* Shaffer[2] has given a man a diet which was free from purins and which contained only 5.9 grams of nitrogen. The individual spent the greater part of six days in bed as a rest period (I). He then occupied himself for five days with laboratory work, which gave a normal period (II). During a final period (III) of four days he worked in the laboratory and performed in addition such mechanical work as that of walking 10 miles. The average of the analyses of the urines of the three periods are given below:

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[1] Zuntz and Schumburg: "Physiologie des Marsches," 1901.
[2] Shaffer: "American Journal of Physiology," 1908, xxii, 445.

UNCHANGED CHARACTER OF THE URINE AFTER MUSCULAR WORK

Period.	Food.		Urine.					
			Nitrogen as:					Sulphur.
	N.	Calories.	Total.	Ammonia.	Creatinin.	Uric Acid.	Rest.	Total.
I. Rest...........	5.9	2300	4.77	0.35	0.605	0.11	0.35	0.438
II. Normal........	6.0	3000	4.40	0.38	0.60	0.106	0.42	0.424
III. Work.........	5.9	3200	3.94	0.42	0.56	0.12	0.42	0.414

Shaffer concludes that if sufficient food be allowed, an increase or decrease of muscular activity has no effect on protein metabolism as indicated by the various quantities of nitrogenous end-products which appear in the urine. Shaffer agrees with Van Hoogenhuyze and Verploegh[1] that with adequate nourishment the creatinin elimination is unaffected by muscular work.

Kocher[2] states that doubling the heat production of the day as brought about by walking 60 kilometers (37.5 miles), *i. e.*, from Munich to the Starnberger See and back, has little or no influence upon the protein metabolism of men, whether the diet consists of starch, sugar and cream, or of meat and fat without carbohydrates.

Bornstein[3] reports continual retention of ingested protein during seventeen days' work, at a time when only protein was administered. The quantity of protein given was large, containing 19.96 grams of N, and the daily work accomplished was moderate, being 17,000 kilogrammeters. The nitrogen retention amounted to 1.475 grams daily, or an addition of 800 grams of "flesh" to the body in seventeen days.

Loewy[4] reaches the same conclusion that long-continued

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[1] Van Hoogenhuyze and Verploegh: "Zeitschrift für physiologische Chemie," 1905, xlvi, 415.

[2] Kocher: "Deutsches Archiv für klinische Medizin," 1914, cxv, 82.

[3] Bornstein: "Pflüger's Archiv," 1901, lxxxiii, 540.

[4] Loewy: "Archiv für Physiologie," 1901, p. 299.

muscular exercise favors protein retention. This suggests the basis of muscular hypertrophy due to physical exercise.

Large protein ingestion, however, is not apparently essential to the full maintenance of physical power. This has been shown by Chittenden,[1] who maintained soldiers and athletes in physical training for months at a time on diets containing between 7 and 10 grams of nitrogen, or about half what the average man takes if the question be left to his taste (see p. 338).

It is evident that the power to accomplish muscular work is not usually derived from protein metabolism, but from the combustion of the non-nitrogenous sugar and fat.

Therefore, physical exercise requiring fat consumption without concomitant destruction of protein must be of the greatest value in the treatment of obesity.

The problem at once arises: What is the relative value of fats and carbohydrates as fuel for the production of mechanical energy by the body?

Zuntz,[2] from experiments made by Heineman, calculates that when carbohydrates predominate in a man's diet an amount of energy above the resting requirement is liberated which equals 9.33 calories for every kilogrammeter of work accomplished, whereas, when fat is given, 10.37 calories are liberated in the performance of the same amount and the same kind of work. The work was done by turning the wheel of an ergostat. Since one kilogrammeter is the mechanical equivalent of 2.35 calories, it is evident that 25 per cent. of the total excess of energy developed by work is convertible into mechanical effect, the balance being dissipated as heat. Similar experiments made by Zuntz on himself showed that 9.39 and 9.33 calories of metabolism were liberated on a fat diet, 10.37 and 10.41 on a carbohydrate diet, when one kilogrammeter of work was accomplished.

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[1] Chittenden: "Physiological Economy in Nutrition," 1904.

[2] Zuntz: "Pflüger's Archiv," 1900, lxxxiii, 557.

There seems to be little difference in the efficacy of the body as a machine, whether fat or carbohydrates are used as fuel.

Heineman[1] remarks that Chauveau's idea that fat must be first converted into sugar before being available for mechanical work can scarcely be valid, for such a conversion of fat carbon into sugar would entail a minimum loss of 29 per cent. of the energy available for mechanical work.

Atwater and Benedict[2] thought that they had confirmed these results, although, unfortunately, the diets provided were not strictly fat-protein and carbohydrate-protein, but were really mixed diets.

Thus J. C. W., during two periods of twenty-two days each, ingested day by day diets which produced the following metabolism as calculated from the body's excreta:

CALCULATED METABOLISM

	Period I. Carbohydrate Diet.	Period II. Fat Diet.
Protein	434 calories.	489 calories.
Fat	1288 "	3190 "
Carbohydrates	3371 "	1465 "
Total metabolism	5093	5144

The average of work accomplished and body heat evolved each day, as measured in the Atwater calorimeter, were as follows:

WORK AND METABOLISM AS DIRECTLY MEASURED

	Carbohydrate Diet.	Fat Diet.
Mechanical work	543 calories.	550 calories.
Body heat	4593 "	4555 "
Total metabolism	5136	5105

The work was done on a stationary bicycle. It is evident that the work could not have been at the expense of protein metab-

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[1] Heineman: "Pflüger's Archiv," 1900, lxxxiii, p. 476.

[2] Atwater and Benedict: "Experiments on the Metabolism of Matter and Energy in the Human Body," 1903, U. S. Dept. of Agriculture, Bulletin 136.

olism; but it is also plain that the work could have been derived from carbohydrate combustion, even in the "fat" diet of Period II.

These experiments, however, were the first to demonstrate exactly that mechanical work was done at the expense of a dynamic equivalent of metabolism—a splendid confirmation of the law of the conservation of energy.

In one other experiment Atwater and Benedict calculated for J. C. W. a metabolism amounting to 9981 calories, divided as follows: Protein, 478 calories; fat, 7744 calories; carbohydrates, 1759. The man worked for sixteen hours on the bicycle. The work done measured an equivalent of 1482 calories; the body heat production was 7382 calories, both of which were measured in the Atwater calorimeter, and the total energy loss reached 9314 calories,[1] a height of metabolism attained also by Maine lumbermen[2] actively employed (see p. 348).

Later work by Benedict and Cathcart[3] includes an experiment on a professional bicycle rider who rode a stationary bicycle for four hours and twenty-two minutes, accomplishing 208,000 kilogrammeters of work during this period, or nearly 13 kilogrammeters per second. The work was the equivalent of more than a "century run," or over 100 miles (161 kilometers). The subject rode to exhaustion. When lying on a couch before the experiment the basal metabolism of this man was 1.14 calories per minute, the R. Q. was 0.85, pulse 63, and respiration 20 per minute. The *basal value for the work experiment* was ascertained by determining the heat production of the man sitting on the bicycle and revolving the wheel when it offered no resistance.

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[1] The calories calculated from the metabolism and those directly measured by the calorimeter did not exactly agree in this particular instance—an exception in a brilliant series.

[2] Woods and Mansfield: U. S. Dept. of Agriculture, 1904, Bulletin 149.

[3] Benedict, F. G., and Cathcart: "Muscular Work," Carnegie Institution, 1914, Publication 187.

The following table presents the results:

METABOLISM DURING A "CENTURY RUN" ON A BICYCLE

SUBJECT, M. A. M.; WEIGHT=65.9 KILOGRAMS.

TIME.	9 A. M.	9.45 A. M.	10.30 A. M.	11.15 A. M.	12.00 NOON.	12.45 P. M.	AVERAGE.
O_2 liters per minute	1.97	1.95	1.97	1.95	2.00	1.90	
R. Q.	0.90	0.91	0.89	0.89	0.97	0.88	0.91
Pulse-rate	129	128	136	156	160		
Respiration rate	30	32	30	36	36		
Work done per minute (calories)	1.96	1.96	1.97	1.94	1.92	1.73	1.95
Mechanical efficiency (per cent.)	34.0	34.4	34.2	34.3	31.4	30.4	
Calories per minute	9.66	9.58	9.65	9.54	10.01	9.28	9.75
Basal value* (calories)	(3.89)	(3.89)	(3.89)	(3.89)	(3.89)		

* No load experiments, without motor.

It is of great interest that the respiratory quotient should have remained at about 0.90 throughout the experiment, which indicated that the body's glycogen was being used in goodly measure throughout the whole period. A calculation shows that 368 grams of glycogen must have been consumed during the time of the ride. The average respiratory quotients of thirty-four days of experimentation with this individual presents the following results:

	REST.	WORK.	AFTER WORK.
R. Q.	0.85	0.88	0.78

The lower respiratory quotient after mechanical work indicates the exhaustion of body glycogen.

The production of 600 calories per hour is probably in the neighborhood of the highest possible maximum of human physical capacity for sustained effort (see p. 431). The mechanical efficiency of 33 per cent. is the same as that previously described by the Zuntz school for raising the body of an individual in mountain ascents. The leg muscles are, therefore, remarkably efficient machines.

This work confirms that of Johansson,[1] that the subjective sense of strain or fatigue has no influence upon metabolism.

Benedict and Cathcart further report a considerable increase in the basal metabolism obtained lying down after severe muscular work, the stimulating influence persisting for five or six hours. For example, a man whose basal metabolism was determined as 1.15 calories per minute rode a bicycle seventy-four minutes, doing work which was the equivalent of 2.06 calories per minute. During four and a half hours of subsequent rest the basal metabolism was determined eight times, and gave values between 1.35 and 1.33 calories per minute in each instance. The rate of the pulse fell from 93 in the first observation to 75 in the last, that of the respiration from 24 to 22.

Mettenleiter[2] states that after hard exercise there is a fall in carbon dioxid tension in arterial blood lasting several days, due to a long continuing slight acidosis (see p. 421).

The stimulus to the increased metabolism is undoubtedly due to lactic acid. The rise in metabolism after giving alanin, which is convertible into lactic acid, is sufficient evidence that lactic acid stimulates metabolism (see p. 240).

Barcroft[3] climbed a straight path to a height of 1000 feet (303 meters) in thirty minutes, a performance which involved only moderate effort. Observations of the carbon dioxid content of the alveolar air and the hydrogen ion concentration of the blood gave the following results:

	CO_2 in Alveoli. Mm.	P_H of Blood.
Normal	40	7.29
After ascent	35	7.09

The difference in acidosis corresponds to an addition of 0.023 per cent. of lactic acid to the blood. In another subject

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[1] Johansson: "Skan. Archiv für Physiologie," 1901, xi, 273; Frumerie: *Ibid.*, 1913, xxx, 409.

[2] Mettenleiter: "Deutsches Archiv für klinische Medizin," 1915, cxvii, 517.

[3] Barcroft: "The Respiratory Function of the Blood," 1914, p. 236.

(Roberts) who made the same ascent the amount of lactic acid necessary to reduce the alkalinity of his blood to the level actually found was estimated at 0.029 per cent., and the increase, as determined by analysis of the blood, amounted to 0.032 per cent. Barcroft gives the following analysis of this state of affairs: During the ascent lactic and carbonic acids, and these only, were added to the blood. On account of the increased hydrogen ion concentration, the hemoglobin at a given pressure takes up oxygen less readily than usual and the respiratory center is stimulated. The increased respirations cause the excessive carbon dioxid produced to be expired, and not only the excess but somewhat more than this; the carbonic acid pressure in the alveolar air therefore falls. Lactic acid, however, is not got rid of so quickly as the carbon dioxid, and is retained. The increase in the hydrogen ion concentration of the blood causes a readier dissociation of the oxyhemoglobin contained in the large and quickly flowing volume of blood which passes through the capillaries of the muscle. At the same time the increased ventilation of the lungs increases the oxygen tension in the alveoli, and, since the absorption of oxygen by the plasma is proportionate to the oxygen pressure, the decreased avidity of hemoglobin for oxygen caused by the increased hydrogen ion concentration is compensated for.

The formation of lactic acid may be attributed to a local anemia during mechanical work. (See Chapter XV.)

Brezina and Kolmer[1] report that the height of the initial respiratory quotients obtained during periods of mechanical work are proportional to the intensity of the work accomplished. When 1.6 calories represented the total metabolism per minute the R. Q. was 0.83, and when the metabolism rose to 10 calories the R. Q. was 0.99. Formation of acid, with the consequent elimination of carbon dioxid from the blood itself, in part explains the high quotient obtained. Increased ventilation and carbohydrate utilization are also undoubtedly

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[1] Brezina and Kolmer: "Biochemische Zeitschrift," 1914, lxv, 16.

contributory. An increased acid formation tends to cause the conversion of liver glycogen into sugar (see p. 421).

Although from Zuntz's work it seems proved that, in furnishing power for mechanical work, carbohydrates and fat are replaceable one for the other according to their dynamic values, there is a well-founded belief that work may be obtained in larger quantity from an individual if carbohydrates be available.

Schumburg[1] finds that ingestion of carbohydrates enables a fatigued muscle to contract more powerfully. Hellsten[2] states that in doing mechanical work in the morning before breakfast, an improved capacity occurs thirty to forty minutes after ingesting sugar.

The ready exhaustion of diabetics who cannot burn glucose confirms this observation.

Lee and Harrold[3] have found evidences of great fatigue in the excised muscles of a cat from which the readily combustible sugar had been removed by rendering the cat diabetic with phlorhizin. Another cat similarly treated, the body of which, however, had been flooded with sugar by ingestion before the animal was killed, showed a much larger capacity for muscular contraction.

The writer[4] while injecting phloretin solutions into the jugular vein of fasting rabbits, diabetic through phlorhizin, noticed that seven out of eight rabbits had convulsions, while normal rabbits were not so affected. Four died and three lost motor control of the muscles of their limbs. In these three there was an increased glucose elimination in the urine on account of the passage of the glycogen content of the organs into the blood, which glycogen would normally be immediately available for muscular activity (p. 107). The animals which survived the convulsions regained control of their muscles

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[1] Schumburg: "Archiv für Physiologie," 1896, p. 537.

[2] Hellsten: "Skan. Archiv für Physiologie," 1904, xvi, 139.

[3] Lee and Harrold: Proceedings of the American Physiological Society, "American Journal of Physiology," 1900, iv, p. ix.

[4] Lusk: "Zeitschrift für Biologie," 1898, xxxvi, 109.

in two to four hours. This indicates a slow preparation from fat of materials available for the production of muscle work.

Schumburg[1] finds that coffee and tea have no recuperative power over the muscles of a fatigued organism except when taken with other foods, and that the stimulating action of alcohol is only temporary. Hellsten,[2] exercising before breakfast, finds that the effect of taking tea is almost negligible, and that the effect of alcohol is at first to increase the muscle power, but that after twelve to forty minutes there is a decrease in power which lasts for two hours. No such depression occurs after taking sugar. It is obvious that alcohol is not beneficial when muscular work is to be accomplished.

The carbon dioxid produced as a result of mechanical work is quickly eliminated through the lungs. Higley and Bowen[3] find that the increased elimination begins twenty seconds after the commencement of bicycle riding and reaches its maximum in about two minutes. At this point it remains constant from minute to minute, provided the same amount of work is done. This principle has been frequently demonstrated by Zuntz and his pupils. It is evident, however, that the quantity of carbon dioxid excretion for the unit of work accomplished will be less during starvation and on a fat diet than when carbohydrates are ingested, by reason of the higher heat value of fat carbon.[4]

Johansson and Koraen[5] have caused a man to raise a weight of 21.7 kilograms ½ meter high, each movement lasting one second, and there being in different experiments 300, 600, 720, and 900 movements per hour. In the trained individual the quantity of increase in the carbon dioxid expired was exactly proportional to the number of the movements in the unit of time. The experiments were performed when food was absent from the intestines.

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[1] Schumburg: *Loc. cit.*

[2] Hellsten: *Loc. cit.*

[3] Higley and Bowen: "American Journal of Physiology," 1904, xii, 335.

[4] Johansson and Koraen: "Skan. Archiv für Physiologie," 1902, xiii, 251.

[5] Johansson and Koraen: *Ibid.*, 1903, xiv, 60.

It has already been shown (see p. 318) that 25 per cent. of the total energy of the increase above the resting metabolism as caused by work is converted into mechanical energy by a person turning the wheel of an ergostat with his arms.

Katzenstein[1] has shown a still more economical utilization of the fuel when the work accomplished is climbing, about 35 per cent. of the total increase in metabolism being then converted into mechanical effect. Walking, the commonest muscular exercise, is accomplished with the greatest mechanical efficiency.

A great many interesting details have been worked out in Zuntz's laboratory by his pupils. The following epitome of long investigations shows the comparative energy equivalents necessary for dog, horse, and man to move 1 kilogram of body weight 1 meter with a given rapidity along a horizontal plane or to lift 1 kilogram of body weight 1 meter high.[2] The experiments were made by placing the individual on a moving platform, the speed and incline of which could be varied.

A study of the table on p. 327 will show that it requires much less energy for a horse to move 1 kilogram of his weight 1 meter horizontally than for a dog to do the same at the same velocity. It also appears that a man of small weight requires more energy to a unit of substance than a man of large size. This rule has been confirmed in dogs by Slowtzoff,[3] who shows that energy amounting to 0.529 kilogrammeter is required for 1 meter horizontal motion by a dog weighing 37 kilograms, and 1.138 kilogrammeters by a dog weighing 5.5 kilograms. Slowtzoff does not find that this variation is proportional to the skin area of the animal.

The table also shows that there is little variation in the dog, horse, and man in the amount of energy necessary to raise 1 kilogram of body substance 1 meter high:

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[1] Katzenstein: "Pflüger's Archiv," 1891, xlix, 379.

[2] Frentzel and Reach: *Ibid.*, 1901, lxxxiii, 494.

[3] Slowtzoff: *Ibid.*, 1903, xcv, 190.

ENERGY REQUIREMENTS OF DIFFERENT ANIMALS IN PERFORMANCE OF THE SAME AMOUNT OF MECHANICAL WORK

Animal.	Weight.	Energy Requirement in Kilogrammeters.		Velocity in Meters per Minute of Horizontal Movement.	Incline of Road in Per Cent. During Climbing Experiment.
		For Moving Horizontally 1 Kg. 1 Meter.	For Raising 1 Kg. 1 Meter High.		
Dog	26.9	0.495	2.954	78.57	17.2
Dog	26.9	0.501	3.259		
Horse	456.8	0.137	2.912	78.57	10.3
Man	55.5	0.334	2.857	74.48	9.6–13.3
	72.9	0.217	3.190	71.32	6.5
	67.9	0.211	3.140	71.46	
	80.0	0.288	3.563	51.23	30.7–62.
	88.2	0.263	3.555	42.34	
	72.6	0.284	2.913	62.04	23–30.5
	81.1	0.231	2.921	60.90	
Man.	80.0	0.244	2.729	56.54	
F. Normal locomotion	86.5	0.219	2.746	66.94	23.3
F. Slow locomotion	86.5	0.233		35.92	
R. Normal	65.8	0.230	2.846	63.95	
R. Slow	65.8	0.251		34.58	

It is possible to calculate the food ration for a march if the figures given in the table be employed. If it be assumed that a man weighing 70 kilograms travels 74.4 meters a minute, he will accomplish 4.46 kilometers or 2.7 miles per hour. If it requires the energy equivalent of 0.217 kilogrammeter to move 1 kilogram of his weight 1 meter, it will require 67,747 kilogrammeters (0.217 × 70 × 4460) to move him 4.46 kilometers—67,747 kilogrammeters being equivalent to 159.205 calories. This is the equivalent of 17.1 grams of fat, which may be added to the maintenance resting dietary requirement to supply the energy necessary for an hour's quiet walk on a level road. If the road be inclined so that the man raises himself 500 meters during the hour's walk, the metabolism will be still further increased. The work of ascent will be his weight multiplied by the height of his climb, or 35,000 kilogrammeters. The expenditure of energy by the body in order to accomplish this work is threefold the work done, or 105,000 kilogrammeters, which equals 246.75 calories, or 26.5 grams of fat. The hour's walk in this case would require the production of an energy equivalent, above the resting metabolism, amounting to that contained in 43.6 grams of fat—that is, 17.1 grams for a forward locomotion of 4.46 kilometers and 26.5 grams to lift the body to an altitude of 500 meters.

In the last-mentioned table it is seen that there is an increase in the metabolism for a unit of horizontal motion when the progress of the individual is very slow. This is explained by the fact that speed of progress was half the normal, was unusual, and forced.

Later work has confirmed the results above enumerated. Thus, Brezina and Reichel[1] find that a man walking on a horizontal plane at a rate not exceeding 80 meters in one minute (3 miles per hour), a rate which they denote as the *maximal economic velocity*, requires 0.5 calorie of energy (= 0.213 kilogrammeter of work) to move 1 kilogram of weight 1 meter, and this rule also applies to weights carried up to about 20 kilograms. This load is about that carried by a soldier. With weights heavier than this there is a slight increase in the quantity of energy required when the individual labors within the limits of the maximal economic velocity. When, however, this velocity is exceeded the expenditure of energy for more rapid walking increases rapidly, and with especial sharpness when heavy loads are carried. A part of the figures is given in the following table:

THE INFLUENCE OF VELOCITY AND OF LOAD IN HORIZONTAL WALKING UPON THE AMOUNT OF ENERGY IN GRAM-CALORIES NECESSARY TO MOVE 1 KG. OF WEIGHT THROUGH 1 METER OF DISTANCE

Distance in Meters per Minute.	Miles per Hour.	Load Equals 3 Kg.	Load Equals 14 Kg.	Load Equals 24 Kg.	Load Equals 36 Kg.	Load Equals 46 Kg.	Load Equals 56 Kg.
44.7– 49.7	1.8	0.48	0.48	0.57	0.59	0.58	0.59
68.9– 73.3	2.7	0.60	0.47	0.52	0.53	0.56	0.59
89.9– 92.0	3.4	0.57	0.62	0.59	0.64	0.81	0.77
111.4–118.1	4.3	0.77	0.93	0.91	0.91		
141.0	5.3	0.93					

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[1] Brezina and Reichel: "Biochemische Zeitschrift," 1914, lxiii, 170.

Benedict and Murschhauser[1] have arrived at essentially the same results as those given above as regards the energy requirement involved in horizontal walking, and they further note that running at the rate of about 5.3 miles per hour is accomplished more economically than walking at the same rate. Their results may be summarized as follows:

	Distance in Meters per Minute.	Gram-Calories for Horizontal Kilogram 1 Meter.
Walking	71.5	0.493
	106.3	0.585
	144.1	0.932
Running	147.5	0.806

The total heat produced when walking at the higher speed was about 600 calories per hour, or about that of the same individual (M. A. M.) when he rode a bicycle, as already described (p. 321). At the lower speed it was found that the process of walking involved a total lifting of the body weight from the ground, amounting approximately to a height of 4 meters per minute. The energy necessary to do this would account for 25 per cent. of the total energy utilized in the muscular complex thrown into action for the purpose of forward progression.

The generalization of Brezina and Reichel is that within the limit of economic maximal velocity the energy requirement of the organism approximates a constant minimum value, which is 0.5 gram-calorie for the forward movement of 1 kilogram of weight 1 meter horizontally. With each meter of velocity above 80 meters per minute the requirement of energy increases 1 per cent. of the initial minimal value. When medium loads (20 kg.) are carried the metabolism increases 2 per cent., and with heavy loads 3 per cent., of the minimal value, per each added meter of velocity above 80 meters per minute.

The rule is that the metabolism increases with speed in

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[1] Benedict, F. G., and Murschhauser: "Energy Transformations During Horizontal Walking," Carnegie Institution, Publication 231, 1915.

horses (1.03 per cent. per meter increase above 78 meters per minute), but this is not seen in dogs.[1]

Brezina and Reichel[2] continued their researches by determining the effect of the gradient of the pathway upon the metabolism of man when walking and carrying different loads. It was found that the maximal work of lifting the body with its load was accomplished at a minimal expenditure of energy when the incline was 20 per cent. and the weight of the load 19 kilograms. However, when walking on inclines with gradients of 10 or 40 per cent., the energy figures were only slightly above the minimal values and the load also made no essential difference. The authors found that to raise 1 kilogram of body substance plus the load carried, required between 9 and 10 calories of energy of metabolism. This represents the conversion of about 25 per cent. of the energy of metabolism into mechanical work. Weights between 3 and 56 kilograms were raised at expenditures of energy directly proportional to the work accomplished.

Katzenstein[3] finds that the metabolism during the descent of a mountain is less by 10 per cent. than the increase caused by walking on a level surface. The muscles which act to inhibit a too rapid descent are not required to be so active as those which give forward impetus to the body on a level road.

This idea has been still further investigated by mountaineers,[4] who compared the actual heat production with the energy of metabolism during one minute for horizontal motion and for ascent and descent of a mountain path which had a 25 per cent. incline. The results were as follows:

	Ascent, 28.8 Meters.	Horizontal, 100 Meters.	Descent, 76 Meters.
Calories of energy of metabolism	69.3	67.8	40.8
Calories of heat liberated	46.9	67.8	85.5

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[1] Zuntz: "Pflüger's Archiv," 1903, xcv, 192.

[2] Brezina and Reichel: "Biochemische Zeitschrift," 1914, lxv, 35.

[3] Katzenstein: *Loc. cit.*, p. 376.

[4] Zuntz, Loewy, Müller, and Caspari: "Höhenklima und Bergwanderungen in ihrer Wirkung auf den Menschen," 1906.

The smallest liberation of heat occurred during the ascent of the mountain at the time when the energy of metabolism was being converted into energy of position.

The largest heat production occurred during the descent of the mountain. The metabolism was the least, but energy of position was converted into heat through the vibration of the body at each footfall.

Zuntz and Schumburg[1] find an increase in the metabolism of a marching soldier if the knapsack be badly placed, or if the body be sore and weary.

Lavonius[2] finds the maximum amount of work attainable by a trained wrestler of great reputation to be the equivalent of 30 kilogrammeters per second.

Details of the effect of position upon the metabolism of individuals have been repeatedly published by Benedict and his pupils. Perhaps the most interesting of these studies may be taken from the work of Benedict and Murschhauser[3] upon the basal metabolism of the professional bicycle rider, M. A. M. The results may thus be summarized:

POSITION.	CALORIES PER MINUTE.	PULSE-RATE.
Lying (basal metabolism)	1.14	
Sitting	1.19	61
Standing, relaxed	1.25	80
Standing, hand on staff	1.26	80
Standing, leaning on support	1.18	78
Standing, "attention"	1.30	73
Standing, swinging arms*	3.13	

* As in rapid walking.

A subject of very great interest is the result of training. It is well known that if a cobbler, for example, be removed from his trade and be compelled to climb a mountain, he will at first be of little use as compared with a Swiss guide. But after continued practice the blood-vessels dilate at once in response to the needs of the muscles and the heart expends less energy; unnecessary motions with the arms and legs are diminished in

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[1] Zuntz and Schumburg: "Studien zu einer Physiologie des Marsches," Berlin, 1901.

[2] Lavonius: "Skan. Archiv für Physiologie," 1905, xvii, 196.

[3] Benedict and Murschhauser: *Loc. cit.*

number; the strain for the accomplishment of a given piece of work diminishes; the thorax enlarges to promote readier respiration; the man becomes "trained," and there is a lessened metabolism for the fulfilment of a definite amount of work.

The experimental measurements of the efficacy of the working organism as described above were made on well-trained men, a difference on account of training having been early recognized by Zuntz.

Bürgi[1] made some investigations upon an individual before and after training for mountain climbing. The ascents were made at different altitudes on the roadbed of mountain railways, and the carbon dioxid elimination was measured. The results are shown in the following table:

EFFECT OF TRAINING ON METABOLISM

Place.	Altitude in Meters.	Incline of Road in per cent.	CO_2 Excretion per Kgm. of Work.	
			Untrained.	Trained.
Brienz	620	17.29	2.430	2.103
Gornergrat	2987	19.3	2.711	2.268
Brienz	690	19.0	2.251	2.063
Gornergrat	3021	19.3	2.445	2.117

It is evident from this that a trained mountaineer accomplishes his work at the expense of less metabolism than does the untrained. Also that at a moderately high altitude (3000 meters = 522 mm. of mercury, barometric pressure) the trained organism is as efficient for mechanical work as at the sea-level, whereas the untrained man required a much greater metabolism to accomplish a unit of work at the higher altitude than at the lower.

Another fact of importance is that the effect of training especially affects the muscles involved in the particular movement, and not those which do not contract. Thus Zuntz[2]

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[1] Bürgi: "Archiv für Physiologie," 1900, p. 509.

[2] Zuntz: "Pflüger's Archiv," 1903, xcv, 200.

found that a dog trained for horizontal motion on a level street required 1179 small calories to move 1 kilogram body weight 1000 meters and 7.668 small calories to raise 1 kilogram body weight 1 meter high. The dog was then gradually trained to ascend an incline. After two years he required only 5.868 small calories to lift 1 kilogram 1 meter, but he required 1343 small calories per kilogram for horizontal locomotion through 1000 meters. Therefore the specifically trained muscles work more economically than those which are at the time but little used.

A man trained for mountaineering will often find himself uncomfortable when walking on a level road. The mountaineer will not find the bicycle an easy means of locomotion,[1] nor will the bicylist unscathed essay the mountain.

A benefit derived from riding a horse is the shaking of the internal organs, which is also achieved by descending a steep pathway. This may be beneficial to the life processes in such a comparatively immobile organ as the liver for example. It also appears to promote a freer evacuation of the bowels.

In swimming there is considerable respiration gymnastics.[2] The water pressure upon the thorax is the equivalent of the weight of an 8-kilogram sand-bag, which the swimmer seeks to counterbalance by increasing the pressure in his lungs through puffing with his lips. By turning over on the back the swimmer removes this respiratory influence. Cold water stimulates metabolism (p. 144), but the effect of the salt in ordinary sea water is certainly negligible.

There can be little doubt that exercise, especially in the open air, strengthens the organism and therefore tends to prolong life. Sometimes muscular exercise is mistakenly considered as favoring intellectual activity. Yet college presidents are not selected from the ranks of prize-fighters.

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[1] Concerning energy expended in bicycle riding see Berg, Du Bois-Reymond, and L. Zuntz: "Archiv für Physiologie," Supplement, 1904, p. 20.

[2] R. Du Bois-Reymond: *Ibid.*, 1905, p. 253.

CHAPTER XII

A NORMAL DIET

The principles of metabolism have been sufficiently explained in the foregoing chapters to make it possible to understand the basis of a diet which shall be physiologically rational.

It has been seen that the average starvation metabolism of a vigorous man at light work and weighing 70 kilograms approximates 2240 calories, or 32 calories per kilogram. It is obvious that this quantity of energy must be contained in the daily food, and a little more to counterbalance the "specific dynamic" or heat-increasing power of the food-stuffs, if the individual is to be maintained in calorific equilibrium. It has been seen that when an average mixed diet is ingested the maintenance requirement is between 11.1 and 14.4 per cent. above the starvation minimum (p. 239). This would amount to from 2488 to 2562 calories, or from 35.5 to 36.6 calories per kilogram of body weight in the case of the individual just referred to.

Rubner[1] is authority for the following table, which indicates the energy requirement of men of various weights while doing light work:

Weight in Kg.	Area in Sq. M.	Calories of Metabolism.	Calories per Kg.
80	2.283	2864	35.8
70	2.088	2631	37.7
60	1.885	2368	39.5
50	1.670	2102	42.0
40	1.438	1810	45.2

Since man through clothing shuts himself off from the reflex action of cold on the skin, the greatest factor which tends to increase his metabolism is mechanical work, and the

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[1] Rubner: von Leyden's "Handbuch der Ernährungstherapie," 1903, Bd. i, p. 153.

total amount of calories required is here dependent on the kind and the amount of the work accomplished. The requirements in this regard have already been discussed.

A point of great interest is that of the proper proportion in which the individual food-stuffs should be put together in making up a ration.

Voit defines a food as a well-tasting mixture of food-stuffs in proper quantity and in such a proportion as will least burden the organism. What is the proper proportion?

Voit[1] gives the following ration for the use of an average laborer, such as a soldier in a garrison—that is, for a man at work from eight to ten hours a day: Protein, 118 grams; carbohydrates, 500 grams; fat, 56 grams. This diet contains 3055 calories.

Such a ration means the food actually ingested. It is also assumed that the food-stuffs are administered in a digestible form, and are therefore completely assimilable. It has already been pointed out in the Introductory Chapter that the feces contain no undigested protein when good food is given. It is, therefore, fallacious to deduct the nitrogen of the feces from the nitrogen of the ingesta in order to determine the amount of protein assimilated. Fecal nitrogen plus urinary nitrogen together represent the waste of assimilable protein nitrogen (see p. 47).

The allowance of 118 grams of protein has provoked much discussion. The original figures were obtained by Voit by averaging the protein metabolism of many laboring men. This requirement of protein was therefore obtained by the statistical method, which simply showed what the average laborer in habit consumed. For the same class of artisan the diet given by Rubner calls for 127 grams of protein; by Atwater, 125 grams; and Lichtenfelt[2] confirms Voit's average as being the quantity of protein taken by laborers in northern Italy.

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[1] Voit: "Physiologie des Stoffwechsels," 1881, p. 519.

[2] Lichtenfelt: "Pflüger's Archiv," 1903, xcix, 1.

For men at hard labor, such as soldiers in the field, even higher quantities of protein are commended—by Voit, 145 grams; by Rubner, 165 grams; by Atwater, 150 grams. These figures again are based on statistics. Woods and Mansfield[1] found that the average protein in the ration of fifty lumbermen is 164 grams.

In striking contrast to this Sivén,[2] at the age of thirty-one and a half years and weighing 65 kilograms, finds he can maintain himself in nitrogen equilibrium for a short period on a diet containing between 4 and 5 grams of nitrogen, or 25 to 31 grams of protein. In fact, in one experiment the food contained 4 grams of nitrogen, of which 2.4 grams only were in 15.4 grams of true protein and the balance in amino-acids and other nitrogenous non-protein matter of vegetable origin. Here nitrogen equilibrium was nearly attained, the nitrogen ingested being 4, and that excreted 4.28 grams. The food given, which was rich in carbohydrates, contained 2717 calories, or 43 calories per kilogram, and the total metabolism, as estimated by respiration experiments, indicated a heat production of 2082 or 32 calories per kilogram. Here was practically nitrogen equilibrium maintained at the minimum level, and a low total metabolism which was largely at the expense of carbohydrates.

It will be recalled that the quantity of nitrogen in the urine in the average fasting man who has been previously well nourished is 10 grams, a minimum which is reducible only by carbohydrate ingestion.

The experiments of Sivén did not satisfy people that a low protein metabolism was compatible with continued health and strength. Munk[3] and Rosenheim[4] both found that dogs given a quantity of protein sufficient only to maintain nitrogen equilibrium gradually lost strength and became afflicted with

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[1] Woods and Mansfield: "Studies of the Food of Maine Lumbermen," U. S. Department of Agriculture, 1904, Bulletin 149.

[2] Sivén: "Skan. Archiv für Physiologie," 1901, xi, 308.

[3] Munk: "Archiv für Physiologie," 1891, p. 338.

[4] Rosenheim: *Ibid.*, p. 341.

digestive disturbances. These experiments fortified the idea of the benefits to be derived from a diet containing more protein than was necessary for the maintenance of nitrogen equilibrium—a *luxus* consumption. Rubner declared that a large protein allowance is the right of civilized man.

The tradition that a continued liberal allowance of protein in a diet is a prerequisite for the maintenance of bodily vigor has been dispelled by Chittenden[1] and his co-workers, of whom Mendel is the most prominent.

Professor Chittenden had suffered from persistent rheumatism of the knee-joint, and determined on a course of dieting which should largely reduce the protein and the calorific intake. The rheumatic trouble disappeared, and minor troubles, such as "sick headaches" and "bilious attacks," no longer recurred periodically as before. "There was a greater appreciation of such food as was eaten; a keener appetite and more acute taste seemed to be developed, with a more thorough liking for simple foods." During the first eight months of the dieting there was a loss of 8 kilograms of body weight. Thereafter for nine months the body weight remained stationary. "Two months of the time were spent at an inland fishing resort, and during a part of this time a guide was dispensed with and the boat rowed by the writer frequently 6 to 10 miles in a forenoon, sometimes against head winds (without breakfast), and with much greater freedom from fatigue and muscular soreness than in previous years on a fuller dietary."

During the period of nine months the nitrogen of the urine was determined daily. The average was 5.69 grams. During the last two months and a half the average elimination was 5.40 grams for a body weight of 57.5 kilograms. Experiments showed that about 1 gram of nitrogen was eliminated in the feces and that nitrogen equilibrium could be maintained with dietaries of low calorific values (1613 and 1549 calories = 28 and 27 calories per kilogram) containing 6.40 and 5.86 grams of nitrogen. These figures correspond to diets containing 40.0 to

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[1] Chittenden: "Physiological Economy in Nutrition," 1904.

36.6 grams of protein instead of the 118 grams honored by habit and tradition. Professor Chittenden proclaimed such a diet as of the highest importance to health.

The case of Chittenden recalls a note from an early convert to the "Graham system" of vegetarianism. Sylvester Graham, in 1829, began the advocacy of moderation in the use of a diet consisting of vegetables, Graham bread (made of unbolted flour), fruits, nuts, salt, and pure water, and excluding meat, sauces, salads, tea, coffee, alcohol, pepper, and mustard. The letter reads as follows:[1] "The first three months of my experiment on the Graham system was attended by a loss of 20 to 30 pounds of flesh. Some of my neighbors expostulated with me—told me I should destroy myself by starvation, and it was even reported in a neighboring town that I had actually died from that cause. But my appetite was increasingly good and my health was increasing, and in a short time my headaches, colds, costiveness, and rheumatism left me entirely, together with my hypochondriacal and gloomy state of mind, and have not returned since, notwithstanding I have been as much exposed to wet and cold as at any period of my life."

Chittenden's experiments were not confined to an individual nor to a single group of individuals. Other experiments were made on professional men, on student athletes in training, and on soldiers under military *régime.* The daily nitrogen in the urine in periods extending from five to nine months averaged as shown in the table on p. 339 in the individuals belonging to the three groups.

At convenient periods during the experiments it was determined that the body was being maintained in nitrogenous equilibrium on the diet which gave rise to the stated amounts of urinary nitrogen (see p. 279).

The professional group alleged a greater keenness for its work, the athletic group won championships in games, and the

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[1] Charles Clapp: "The Graham Journal of Health and Longevity," Boston, 1837, i, 57.

soldiers maintained perfect health and strength, many professing repugnance to meat when they were allowed it after five months of practical abstinence.

PROFESSORS AND TEACHERS.		UNIVERSITY ATHLETES.		UNITED STATES SOLDIERS.	
Weight in Kg.	N in Urine in G.	Weight in Kg.	N in Urine in G.	Weight in Kg.	N in Urine in G.
57.0	5.69	71.0	9.37	62	7.42
70.0	6.53	61.0	10.41	59	7.03
65.0	7.43	78.0	8.88	60	7.26
65.0	8.99	83.0	9.04	58	8.17
61.5	8.58	62.0	7.47	60	8.39
		56.0	7.58	53	7.13
		73.0	10.09	71	8.91
		75.0	11.06	72	7.84
				62	8.05
				59	7.38
				55	8.25
				65	8.08
				57	8.61

Although it is possible that the alleged improved mental condition[1] may have been due to suggestion (p. 486), still the fact remains that it has been proved by Chittenden's work that the allowance of protein necessary for continued health and strength may be reduced during many months to half or less of what the habit of the appetite suggests.

It remains to be seen whether this quantity of protein in the ration, which is not greater than the body would metabolize in starvation, is advisable as a program for the whole of one's adult life.

The foods with the strongest flavors are meats, which therefore add relish to a repast and stimulate the digestive secretions.

Chittenden believes that the large quantity of protein in an ordinary diet is due to self-indulgence. He protests against such indulgence, and thinks that a needless strain is thereby imposed upon the liver, the kidneys, and other organs con-

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[1] Chittenden: *Loc. cit.*, p. 51.

cerned in the transformation and elimination of the end-products of protein metabolism.

Another advocate of a low protein dietary has arisen in the person of Hindhede,[1] who advocates as ideal a diet consisting of bread, potatoes, and fruit, together with a small quantity of milk when this latter is obtainable. It is avowedly a "back-to-the-farm" dietary. Splendid health, both of body and mind, and the peasants' comparative immunity to indigestion, kidney and liver disease, to diabetes, as well as an absolute immunity to gout, is the alluring prospect held out by the following dietary:

Graham bread	500 grams.
Potatoes	1000 "
Vegetable margarin	150 "
Apples	600 "
Milk	500 c.c.

Such a diet gives a urine which dissolves uric acid readily, the addition of the apples appreciably increasing this power. Hindhede also states that the ingestion of 5 kilograms of tomatoes with 600 grams of Graham bread and 150 grams of margarin daily for four days also produces a urine having a good solvent power over uric acid.

In analyzing the effect of the factors of the bread-potato-fruit diet Hindhede found that an exclusive bread diet gave a urine which exhibited a strong tendency to deposit uric acid, and notes that the Russian peasant, who works fourteen to sixteen hours daily and lives almost exclusively upon bread, frequently has gravel. On the other hand, potatoes when ingested yield a urine which is very slightly acid, often on the border-line of alkalinity, and one which has a very great solvent power over uric acid.

It is a curious fact that the potato, long proscribed by many physicians, has decided therapeutic value. Some one has remarked, "One meets the potato today in the very best circles."

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[1] Hindhede: "Skan. Archiv für Physiologie," 1912, xxvii, 87.

Hindhede[1] reports the following results upon the daily nitrogen balance after giving various forms of bread during periods of eight days:

		In Diet		
		Calories.	N Grams.	± N to Body, Grams.
Schwarzbrot	1000 g. + fat 120 g......	3200	12.1	+0.3
White bread	900 g. + fat 120 g......	3640	13.2	+0.6
Rye bread	1000 g. + fat 135 g......	4000	12.8	−1.7
Graham bread	1000 g. + fat 140 g......	3800	15.1	+0.4

These results show a favorable utilization of bread protein.

Concerning the utilization of potato protein Hindhede[2] reports the following remarkable experiment: An individual partook of a diet of 2 to 4 kilograms of potatoes with some margarin daily during a period of nearly three hundred days. The potatoes were well boiled in water and the water in which they were cooked was drunk on account of valued salts therein contained. The rule was to eat only when hungry. Potatoes could be eaten at the rate of 100 grams in four minutes. Stools were passed once every three or four days, but there was no constipation. During a period of one hundred and seventy-eight days 6.05 grams of nitrogen and 3725 calories were contained in the daily diet, and there occurred an average daily loss of body nitrogen of 0.42 gram. During a second period of ninety-five days, when mechanical work was performed, there were 8.45 grams of nitrogen and 4900 calories in the daily diet and the daily loss of body nitrogen was 0.36 gram. During these ninety-five days the food supply consisted of 350 kilograms of potatoes and 22 kilograms of fat taken in the form of margarin.

Hindhede states that he "feels weak" after taking much meat.

One may pass now to the other side of the story.

Lichtenfelt[3] shows that while there is no statistical difference in the height of individuals as due to occupation, still the people of southern Italy are not so large nor so well

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[1] Hindhede: "Skan. Archiv für Physiologie," 1913, xxviii, 165.

[2] Hindhede: *Ibid.*, 1913, xxx, 97.

[3] Lichtenfelt: "Pflüger's Archiv," 1905, cvii, 57.

developed physically as their fellows of northern Italy. He explains this stunted growth as due to a low protein and calorific intake in the food.

Albertoni and Rossi[1] describe how the poorest Italian peasants in southern Italy live on cornmeal, green stuffs, and olive oil, and have done so for generations. There is no milk, cheese, or eggs in their dietary. Meat in the form of fat pork is taken three or four times a year. Cornmeal is taken as "polenta," or is mixed with beans and oil, or is made into cornbread. Cabbage or the leaves of beets are boiled in water and then eaten with oil flavored with garlic or Spanish pepper. The average elimination of urinary nitrogen of 13 persons in three families when taking this diet was for men 8.1 and for women 6.7 grams of nitrogen daily. The investigators, furthermore, considered a family of 8 individuals of whom 2 were children. The annual income was 424 francs or $84. Of this, 3 cents per day per adult was spent for food and the remaining $\frac{3}{5}$ cent daily was spent for other purposes. The addition of 100 to 200 grams of meat daily to the diet of each of these individuals increased their muscular power, and the investigators believed that such an addition was essential to mental health as well.

The position of the food extremists was powerfully attacked by Rubner,[2] whose general tone was in advocacy of variety in the dietary of man in accordance with the then prevailing habits and certainly without attempting to conform to a protein minimum. Since the outbreak of the war, with the food restrictions which have accompanied it, Rubner has become convinced that a restricted protein dietary is without harmful influence. This information has been given the author through a reliable source. For Rubner's ideas of practical food reform see p. 570.

Hirschfeld[3] finds that the actual ration of a German soldier

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[1] Albertoni and Rossi: "Archiv für experimentelle Pathologie und Pharmakologie," 1908, Supplement, p. 29.

[2] Rubner: "Ueber moderne Ernährungsreformen," Berlin, 1914.

[3] Hirschfeld: "Archiv für Physiologie," 1903, p. 380.

contains 98 grams of protein, with no untoward results. He states that writers on economics, who believe the German populace underfed because they do not have 118 grams of protein daily, are unduly pessimistic.

Although, as has been stated, the battleground has been over the allowance of 118 grams in Voit's dietary, it will be surprising to many to learn that Voit himself said little on the subject. He[1] showed that a vegetarian can live in nitrogenous equilibrium on a diet containing 48.5 grams of protein and that an active working man weighing 74 kilos may get along on less than 118 grams. He discouraged the tendency to eat meat in excess. He also discouraged the practice of vegetarians who overload the digestive tract with the coarser kinds of vegetable foods which leave large indigestible residues.

It is not to be denied that 50 grams of protein (containing 8 grams of nitrogen) are apparently able to maintain the adult body machine in perfect repair. Vegetarians, fruitarians[2] (who live on fruit and nuts), and vigorous adults, who largely exclude protein from the diet, are evidently able to live in health and strength upon this quantity. It must be, however, that more than this amount is advisable during growth or convalescence from wasting disease, or during the muscular hypertrophy which accompanies preliminary training for athletic effort.

Abderhalden[3] mentions the fact that since various body tissues are constructed of different proteins, therefore a large variety of amino-acids in sufficient quantity must be available for their proper replenishment. Hence, it is reasonable to assume that an excess of food protein is essential to supply the special amino-products for the synthesis of the characteristic proteins of the blood-serum and those of the different organs.

It is certain that large ingestion of protein in hot weather increases the heat production with accompanying increase in

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[1] Voit: "Zeitschrift für Biologie," 1889, xxv, 278.

[2] Jaffa: U. S. Department of Agriculture, 1903, Bulletin No. 132.

[3] Abderhalden: "Zentralblatt für d. ges. Physiol. und Path. d. Stoffwechsels," 1906, i, 225.

perspiration (p. 235). Meat should therefore be avoided in hot weather. In cold weather such an extra heat production may produce a pleasurable sensation of warmth. Dr. Folin, in personal conversation with the writer, said that a dietary of carbohydrates, fat, and low protein was easily borne by an individual during the summer, but during the winter the man complained of his sensitiveness to cold when taking the same diet.

Ranke[1] describes experiments on himself (weight = 73 kilograms) during the hottest months of summer weather in Munich, at which time he partook of an ample diet, rich in protein (135 grams), containing 3300 calories—a diet which he had enjoyed during the preceding winter. He had to force himself to eat. He was first attacked by catarrh of the stomach, from which he recovered by dieting, and subsequently became infected by diphtheria. He had formerly suffered from catarrh of the stomach while residing in the tropics. The excess of food, and especially of protein, threw an unnecessary burden upon the heat-regulating apparatus which would not have taken place had the dictates of the appetite been allowed full sway and had the ration voluntarily been reduced.

From the knowledge at hand there appears to be no strongly substantiated argument why that portion of mankind living in a cool climate should not follow the general custom of taking 100 grams of protein, more or less, in moderate accordance with the dictates of their appetites. Everyone knows that excessive ingestion of highly flavored meats results in jaded appetite, an automatic signal of excess.

A similar excess of food when given to dogs results in vomiting. Rubner[2] says that many years of experience with dogs leads him to believe that appetite and capacity for digestion and absorption depend on the dog's requirement for energy in his given state of nutrition. A diet which a dog will greedily

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[1] Ranke: "Zeitschrift für Biologie," 1900, xl, 299.

[2] Rubner: "Energiegesetze," 1902, p. 83.

devour when in a room at a temperature of 0° he will in part refuse when at a temperature of 33°.

Evvard[1] writes: "When the appetite is given full control of what shall be eaten it is surprising to note how pigs naturally select the specific feeds which swine herdsmen have long since approved of as the best, and, what is equally surprising, the pigs show a marked avoidance of those feeds usually considered as ill adapted to swine."

While the protein quantity in the diet may vary within wide limits with the taste, the purse, or the fad of the individual, the quantity of energy required by the organism is a remarkably constant factor, being 35 calories per kilogram of body weight in the average man doing light work on a mixed diet. Comparatively little of this energy is furnished by protein.

In a fasting individual protein furnishes 13 and fat 87 per cent. of the total heat given off from the body.

In Voit's medium mixed diet, designed for a laboring man, the 118 grams of protein furnish about 15 per cent. of the total of 3055 calories.

In such an experiment as Sivén's, mentioned on page 336, which represents a very low level of nitrogen equilibrium, the 25 grams of protein ingested furnished 100 calories out of 2717 ingested in the food, or 3.6 per cent. However, since the total metabolism was measured as 2082 calories, the protein furnished approximately 5 per cent. of this energy.

Chittenden[2] gives a dietary containing 50 grams of protein and 2500 calories as sufficient for a soldier at work. This allows 8 per cent. of the total energy in protein. These data may be thus summarized:

	Grams of Protein in Diet.	Calories from Protein Metabolism in Per Cent.	Calories from Fat and Carbohydrate Metabolism in Per Cent.
Starvation	0	13	87
Voit's standard (liberal protein)	118	16	84
Chittenden's standard (reduced protein)	50	8	92
Sivén's minimum	25	5	95

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[1] Evvard: "Proceedings of the Iowa Academy of Science," 1915, xxii, 400.
[2] Chittenden: *Loc. cit.*, p. 254.

The energy other than that contained in protein may be given as carbohydrates or as fat. Voit allows a laborer 500 grams of starch (2050 calories, or 67 per cent. of the total) as the quantity which the intestinal canal may readily digest, and adds 56 grams of fat (521 calories, or 17 per cent. of the total) to the diet.

It has already been observed that half the energy may be given in fat and half in carbohydrates without affecting the carbohydrate power of economy over the protein metabolism (see p. 270).

This part of the subject really becomes a mere matter of calculation of the requirement of the resting organism, and the addition thereto of sufficient energy to accomplish the mechanical work.

How this is done has already been set forth in another chapter. A bicyclist riding for sixteen hours may have a metabolism amounting to 9000 calories daily, and the average ration of a Maine lumberman may rise to a value of 8000 calories. Champion wrestlers in a world's contest[1] may ingest daily during their periods of effort diets containing protein 217.9 grams (35.1 grams of N); fat, 259.5 grams; carbohydrates, 431 grams; together, 5070 calories; or protein, 182.2 grams (29.2 grams N); fat, 204.6 grams; carbohydrates, 392.3 grams; together, 4254 calories. Much cream was taken by these last-named individuals.

Chittenden[2] has fallen into error in the commendation of 2500 to 2600 calories as an ample diet for a soldier at drill. For himself, pursuing a sedentary life, Chittenden prescribes 2000 calories, or 35 per kilogram, while Mendel requires 2448 calories, or 35.3 calories per kilogram. These are entirely normal values for people at light work. In the earliest calculations of Voit, in 1866, it was shown that a man of 70 kilograms on a medium mixed diet produced 2400 calories, or 34.3 calories per kilogram; and Rubner allows 2445 calories to men

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[1] Lavonius: "Skan. Archiv für Physiologie," 1905, xvii, 196.

[2] Chittenden: *Loc. cit.*, p. 254.

of 70 kilograms weight engaged in occupations involving light muscular work—such men as writers, draughtsmen, tailors, physicians, etc. But the soldiers under Chittenden were put for two hours in the gymnasium, then apparently drilled for one hour, and walked another hour. This physical work requires increased energy from metabolism. It has been shown that to walk 2.7 miles in an hour on a level road requires an increased metabolism of 159.2 calories in a man weighing 70 kilograms. If a soldier during four hours actually expended this equivalent mechanical energy in excess of the amount of Professor Mendel in his laboratory, then his metabolism would be larger than Professor Mendel's by 637 calories, or he would have a total metabolism of 3085.

In Chittenden's experiments there was no analysis of the expired air, and conclusions are drawn from the maintenance of body weight.

Several of the larger-sized soldiers (those who weighed 70 kilograms) lost between 3.5 and 8.5 kilograms of body weight during the experiments. Fritz, weighing 76.0 kilograms, lost 3.6 kilograms in five months. Had this all been fat, one can estimate that its heat value would have been 33,480 calories, or an available daily combustion of body substance equal to 223 calories. Conclusions drawn from weight alone can be of only the roughest character (see p. 273).

For ordinary laborers, working eight to ten hours a day, such as mechanics, porters, joiners, soldiers in garrison, and farmers, 3000 calories does not seem an excessive quantity.

Rubner's diet calls for 2868 calories. Chittenden's allowance (2500–2600) is too low, while Atwater's (3400) approximates that required by a farmer.

A third class are men at hard labor, such as soldiers in the field, shoemakers, blacksmiths, etc. For these Voit allows a dietary containing 3574 calories; Rubner, 3362 calories; and Atwater, 4150 calories. The differences in these figures are merely differences in the quantity of work alone.

In almost all the rations given carbohydrates do not exceed 500 grams. The remainder is made up of fat.

Atwater[1] reports the following dietaries for farmers:

	Calories.
Farmers in Connecticut	3410
" Vermont	3635
" New York	3785
" Mexico	3435
" Italy	3565

To this list may be added for farmers in Finland 3474 calories, as found in the exhaustive studies of Sundström.[2] He states that the diet of the average Finnish peasant contains 136 grams of protein, 83 grams of fat, and 580 grams of carbohydrates, which corresponds to a division of calories so that protein furnishes 15 per cent., fat 21 per cent., and carbohydrates 64 per cent. of the total. He notes that if the peasant's requirement of energy were taken in rye bread alone 124 grams of protein would be ingested with it, whereas if a milk diet covered the requirement 195 grams of protein would be taken. He, therefore, sees no outlook for a low protein dietary among the poorer classes, that have hard work to do and must ingest large quantities of food fuel.

Woods and Mansfield[3] report a dietary study of a camp of fifty Maine lumbermen actively engaged in chopping and yarding logs. The investigation continued for six days. The daily average ration per man was as follows: Protein, 164.1 grams; fat, 387.8 grams; carbohydrates, 982.0 grams; calories, 8083 This dietary would appear almost fabulous were it not for the fact that Atwater has actually shown that a metabolism equivalent to 9300 calories a day may be produced by a man riding a stationary bicycle for sixteen hours.

Becker and Hämäläinen[4] in Finland have shown how much energy is needed by people in various occupations. The women may be first considered. The work day was of eight hours:

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[1] Atwater: Report of Storr's Agricultural Station, 1902–03, p. 135.

[2] Sundström: "Untersuchungen über die Ernährung der Landbevölkerung in Finland," 1908.

[3] Woods and Mansfield, *Loc. cit.*

[4] Becker and Hämäläinen: "Skan. Archiv für Physiologie," 1914, xxxi, 198.

A seamstress sewing with a needle required 1800 calories.

Two seamstresses, using a sewing machine, required 1900 and 2100 calories, respectively.

Two bookbinders required 1900 and 2100 calories.

Two household servants, employed in such occupations as cleaning windows and floors, scouring knives, forks, and spoons, scouring copper and iron pots, required 2300 to 2900 calories.

Two washerwomen, the same servants as the last named, required 2600 and 3400 calories in the fulfilment of their daily work.

Concerning the fuel requirement for the occupations of men:

Two tailors required 2400 to 2500 calories.

A bookbinder required 2700 and a shoemaker 2800.

Two metal workers, filing and hammering metals, required 3100 and 3200 calories.

Two painters, occupied in painting furniture, required 3200 and 3300 calories, and two carpenters engaged in making tables required the same amount of energy.

Two stonemasons chiseling a tombstone needed 4,300 and 4700 calories.

Two men sawing wood required 5000 and 5400 calories.

The proverbial reputation of sawing wood as a strenuous occupation has here its scientific verification and explains the disinclination of the hungry to engage in this useful occupation, as well as the unpopularity of charitable wood yards.

Carpenter[1] has investigated the energy required for typewriting. He finds that the increase in oxygen absorption, above the amount when the typist is sitting and reading, amounts to about 2.47 grams, or the equivalent of 8 calories per thousand words when the speed is fifty words per minute. This would aggregate 24 calories per hour or 192 calories for eight hours. This quantity of energy is about the equivalent of that necessary for the forward progression of an average man walking horizontally for one hour and ten minutes at

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[1] Carpenter: "Journal of Biological Chemistry," 1911, ix, 231.

a speed of 2.7 miles an hour; the expenditure of energy in typing is therefore slight.

A lower ration than the lowest here mentioned may be allowed to one who is confined to his bed (p. 110). In many hospitals, however, it has been found that liberal feeding of the very poor is often better than medicine.

The "standard" dietaries are given below, not because they are inflexible requirements in any sense of the word, but merely for the convenience of the reader. The individual standard will ever be controlled by climate, the amount and kind of mechanical effort; by appetite, purse and dietetic prejudice.

STANDARD DIETARIES FOR A MAN OF 70 KILOGRAMS
(Weights in Grams)

	Voit.	Rubner.	Atwater.
Light work:			
Protein	..	123	100
Fat	..	46	*
Carbohydrates	..	377	*
Calories	..	2445	2700
Medium work:			
Protein	118	127	125
Fat	56	52	*
Carbohydrates	500	509	*
Calories	3055	2868	3400
Hard work:			
Protein	145	165	150
Fat	100	70	*
Carbohydrates	500	565	*
Calories	3574	3362	4150

*Carbohydrates and fats to make up the fuel value.

Rubner[1] cites the following food values consumed daily per inhabitant of different cities, based upon municipal statistics of gross consumption:

MUNICIPAL FOOD STATISTICS

	Protein.	Fat.	Carbohydrates.	Calories.
	Grams.	Grams.	Grams.	
Königsberg	84	31	414	2394
Munich	96	65	492	3014
Paris	98	64	465	2903
London	98	60	416	2665

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[1] Rubner: von Leyden's "Handbuch der Ernährung," 1903, i, 160.

In contrast to this, comparative uniformity hospital dietaries, as regulated by the management of such institutions, vary greatly.

Rubner[1] cites the following hospital dietaries:

HOSPITAL DIETARIES

	Protein.	Fat.	Carbohydrates.	Calories.
	Grams.	Grams.	Grams.	
Munich	92	54	157	1381
Augsburg	94	57	222	1823
Halle	92	30	393	2267
England	107	69	533	3266

An interesting study of the dietary of a poorhouse in Helsingfors, Finland, was made by Elizabeth Koch.[2] A total of 3355 calories was offered to each of five old men daily and 2430 were taken per person. Of the food offered, 1500 calories were contained in bread. The dietary was thus arranged:

Breakfast.	Daily: 200 gm. potatoes; ⅓ liter skimmed milk; 40 gm. butter. Four times a week, 50 gm. salt fish (Strömling); bread, 200 gm.
Dinner.	Daily: 200 gm. bread. Four times weekly, 100 gm. meat; 200 gm. potatoes. Twice a week bean soup. Beets and barley also furnished.
Supper.	Mostly bread, skimmed milk, and wheaten grits.

When taking this diet the inmates of the institution consumed an average of 106 grams of protein, 55 grams of fat, 361 grams of carbohydrates, and 34 grams of salts. The total quantity of milk offered, amounting to between 667 and 1000 c.c. daily per person, was in each case completely taken. Old men of seventy-five years took a fair quantity of food, as appears from the following analysis:

	Age.	Weight.	Height.	Calories in Food.	Calories per Kg.
	Years.	Kg.	M.		
M.	54	62.5	1.64	2307	36.9
J.	60	72.5	1.76	2790	38.5
Mu.	70	70.5	1.65	2565	36.4
A.	75	65.0	1.64	2379	36.5
L.	79	60.0	1.65	2108	35.1

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[1] Rubner: *Loc. cit.*, p. 157.

[2] Koch, E.: "Skan. Archiv für Physiologie," 1911, xxv, 315.

The author concludes that the quantity of food needed by old men is slightly below the normal (see p. 129).

The population of a city will ordinarily sustain itself in accordance with its needs. In public institutions, however, such as poorhouses, prisons, asylums, hospitals, and in military and naval establishments, scientific knowledge of the needs of the individual becomes a very important consideration. The prolonged endurance of an army of soldiers is just as dependent on an ample army ration as is the battleship dependent on its supply of fuel. Not only the quantity of the food makes for the well-being, but it must taste well. No amount of actual fuel value could compel the American soldiers of the Spanish-American war to eat the "embalmed beef" furnished by the Government. The flavor is to the man what oil is to the machinery of the battleship. Without flavor in the food the digestive apparatus does not run smoothly. In ordinary civilized life even psychical influences act. The cloth on the table must be spotless, and the environment inviting.

In the process of manufacture of Liebig's extract of beef muscle creatin is largely converted into creatinin. Such an extract, which contains also xanthin, is not strictly a food, since its constituents are largely ready for elimination in the urine.[1] Bürgi[2] shows that if meat extract be administered it is excreted in the urine, excepting 4.57 per cent. of its nitrogen, 14.85 per cent. of its carbon, and 17.55 per cent. of its energy content.

Its value lies in its *flavor*, which promotes the proper flow of the digestive juices.[3]

It may be incidentally remarked that the principal value of many "patent" foods, "invalid" foods, etc., lies in their flavor. If agreeable to the taste of the individual they usually afford a harmless indulgence. That beef, milk, cream, butter, and rice are quite as suitable for all the purposes of proper living is a fact not sufficiently advertised. The old-time fraud of

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[1] Rubner: "Zeitschrift für Biologie," 1883, xix, 343.

[2] Bürgi: "Archiv für Hygiene," 1904, li, 1.

[3] Voit: "Stoffwechsel," 1881, p. 449.

"patent" foods being "brain restorers" is as foolish a lie as can be written.

One takes as food milk, eggs, various meats, such as beef, veal, pork, mutton, fish; also cereals, such as bread, rice, corn, macaroni, beans, and peas. Sometimes alcoholic beverages are added. The calorific values may be calculated by determining the composition of the various nutrient materials by analysis and by multiplying the number of grams of each constituent by the factor which represents its fuel value to the organism (see p. 42).

As a simple illustration of this the following experiment of Rubner[1] may be cited: A man weighing 46 kilograms ate nothing but eggs for two days—22 on the first day and 20 on the second. The 22 eggs contained 1017.4 grams of material; the 20 eggs, 878.8 grams, an average of 948.1 grams per day. Since 100 grams of egg contain 14.1 grams of protein and 10.9 grams of fat, 948.1 grams would contain a daily allowance of 133.6 grams of protein and 103 grams of fat. If Rubner's standard values for the energy content are used, the result will be as follows:

133.6 grams protein × 4.1 = 547 calories.
103.3 grams fat × 9.3 = 961 calories.

Total............... = 1508 calories,
or 33 calories per kilogram.

This dietary of eggs was, therefore, nearly sufficient for the fuel requirement of this undersized individual. Notwithstanding the large amount of protein in the dietary there was a loss of body protein equal to 7.5 grams per day.

The results of an exclusive milk diet are thus summarized by Rubner:[2] Milk (2438 grams), containing 84 grams of protein and two-thirds of the requirement of energy for the individual, produced a deposit of protein equal to 6.7 grams daily (p. 279). To cover a requirement of 2400 calories daily 3410 grams of milk would be needed, which contain 140 grams of protein.

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[1] Rubner: "Zeitschrift für Biologie," 1879, xv, 127.

[2] Rubner: von Leyden's "Handbuch der Ernährungstherapie," 1903, i, 132.

For a laboring man with a requirement of 3080 calories, 4380 grams of milk with 180 grams of protein would be necessary.

Thomas[1] drank 10.7 liters of whole milk (6781 calories) in one day, taking it up to the limit of his capacity. Of 53.3 grams of nitrogen in the milk, 28.7 grams appeared in the urine of the day and 21.1 grams were added to the body. Of 67.4 grams of salts contained in the milk, 36.9 grams were present in the urine of the twenty-four-hour period and 29.5 grams were passed in the feces attributable to the diet; the power to absorb such a diet was therefore great. Dried milk powder preparations were absorbed with as great ease as whole milk.

It is evident that milk with its high protein content is a food *par excellence* for the growing organism or for the invalid convalescing from wasting disease. It contains too large an amount of protein for a normal adult. A mixture of milk, toast, and cream (creamed milk-toast) may produce a modified milk diet of proper value and easy digestibility. An exclusive milk diet contains too little iron for the needs of a normal adult.

Moritz[2] recommends milk alone in treatment of obesity, in quantities varying between 1.5 and 2.5 liters daily. The normal weight in kilograms of the individual is calculated from his height, and each kilogram of such weight is provided with 16 to 17 calories in the diet, an amount which is contained in 25 c.c. of milk. Should the normal weight be 80 kilograms, 2000 grams of milk are administered daily in five portions. Such treatment brings about a considerable loss in body weight, and, although some body nitrogen is lost, a state of weakness does not ensue.

Rubner finds that 1500 grams of good white bread containing 104.4 grams of protein will maintain a working man in nitrogenous and calorific equilibrium.

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[1] Thomas: "Archiv für Physiologie," 1909, p. 417.

[2] Moritz: "Münchener medizinische Wochenschrift," 1908, lv, 1569.

Thomas[1] took on three successive days an average of 2760 grams of fresh bananas which were not completely ripe, and to this he added 300 grams of sugar. This gave a total intake of 4.32 grams of nitrogen and 2741 calories daily. Although a preliminary diet of starch and sugar had reduced the urinary nitrogen to 3 grams at the beginning of the experiment, nitrogen equilibrium could not be obtained when the above noted amount of bananas was ingested. The unripened starch of the banana is eliminated in the feces. Ripe banana in which almost all the starch has been converted into glucose is very completely digestible. Whereas five parts of potato protein may replace four of body protein in establishing nitrogen equilibrium, the protein of banana is not so efficient. Yet in tropical countries, such as the sea-coast of East Africa, the Congo, and in the Pacific Islands, during the six months of the rainy season (in which the banana is ripe), it furnishes almost the exclusive diet of the natives. It is preferred to potatoes because it can be obtained almost without labor. Banana flour is also prepared in these localities by drying unripe bananas in the sun.

If water be taken when the stomach is empty it quickly passes through the pylorus into the intestine. Taken with food, however, its exit from the stomach is considerably delayed; the delay accounts for some of the pleasure of afternoon tea when taken with toast. Beer remains in the stomach longer than water, and this may be due to the extractive substances or to a narcotizing effect upon the musculature of the stomach.[2]

Atwater and Benedict[3] have conclusively shown that alcohol may be used in the economy in place of isodynamic quantities of carbohydrates and fats. The following table shows the average of experiments on a resting individual which lasted twenty-three days:

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[1] Thomas: "Archiv für Physiologie," 1910, Suppl., p. 29.

[2] Gröbbels: "Zeitschrift für physiologische Chemie," 1914, lxxxix, 1.

[3] Atwater and Benedict: "Memoirs of the National Academy of Sciences," Washington, 1902, viii, 231.

INFLUENCE OF ALCOHOL ON METABOLISM

	Duration in Days.	In the Food in Grams.			Alcohol.	Cal. in Food.	Cal. of Metabolism.	Protein Balance.
		Protein.	Fat.	Carbohydrates.				
Ordinary diet....	13	114	69	354	..	2496	2221	−2.0
Alcohol-containing diet.......	10	115	47	273	72.2	2488	2221	−3.8

Atwater and Benedict employed diets containing about 2500 calories for a man at rest and 3500 for a man at work. During the alcohol days 500 of the calories were supplied in 72 grams of alcohol, or about what is contained in a bottle of claret. The metabolism of the individual as expressed in calories was unchanged by the addition of alcohol to the diet. The alcohol was given in six small doses and 98 per cent. was burned by the organism.

On the ordinary diet 33.7 grams of fat were daily added to the body, and on the alcohol days 34.1 grams. These very valuable observations make it evident that alcohol is not a direct cause of obesity. If, however, a young man having acquired certain dietary habits at home continues the same diet at college and begins to drink "in moderation" besides, his increasing rotundity as he returns on his vacations can be readily explained by the sparing influence of alcohol upon the fat in his diet.

A liter of German beer contains 3 to 4 per cent. of alcohol and 5 to 6 per cent. extractives. It yields 450 calories to the body, only half being derived from alcohol, the rest from the dextrin and protein-like extractives. Here is a material whose "fattening" properties may be very highly considered.

It is reported that alcohol is present in normal human blood to the extent of 3 parts in 100,000. When alcohol is drunk it passes into the blood as such, and as much as 2 parts in 1000 has been found in the blood of a drunken man by

Schweisheimer.[1] According to this author, the intensity of the drunkenness depends on the concentration of alcohol in the blood. A maximum concentration is reached about an hour and a half to two hours after drinking and may remain high for five hours. Those who are accustomed to alcohol oxidize it all in seven and a half hours, whereas those who have been abstainers require twice that time.

It is interesting that although alcohol ingestion reduces the respiratory quotient after it has been given, it has never been found to reduce it to such an extent as to indicate that it is the main source of the energy supply of the body.

An experiment by Durig[2] showed that after giving 30 grams of fructose to a man every hour the respiratory quotient rose to unity; but if 30 c.c. of alcohol were given about the same time the respiratory quotient was depressed to about 0.80. Alcohol was, therefore, in large measure oxidized instead of sugar, but the respiratory quotient did not approximate 0.67, the quotient for alcohol itself, as would have been the case if the source of energy had been exclusively alcohol (see p. 298). These authors find no summation of dynamic effect when alcohol and carbohydrate are oxidized together (see p. 298).

Völtz and Dietrich[3] have given dogs 2 c.c. of alcohol per kilogram of body weight. After ten hours only 73 per cent. of the material had been oxidized, or enough to provide for 43 per cent. of the energy requirement of the time. About 90 per cent. was oxidized in fifteen hours, but it required about eighteen to twenty hours for the dog to rid himself of the material. Alcohol, therefore, is not a quickly oxidizable substance, but it remains in the blood a long time. Although sugar may entirely displace fat metabolism, alcohol can only in part displace carbohydrate from its part in metabolism.

All alcoholic beverages are taken with a twofold object: first, the desire for flavor, and second, for stimulation; their

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[1] Schweisheimer: "Deutsches Archiv für klinische Medizin," 1913, cix, 271.
[2] Tögel, Brezina, and Durig: "Biochemische Zeitschrift," 1913, l, 298.
[3] Völtz and Dietrich: *Ibid.*, 1914, lxviii, 118.

food value, as above described, is usually little considered. In general, it may be said that alcohol as a stomachic is valueless when the gastric juice is normal, but is beneficial in cases of supersecretion, hypochlorhydria, and loss of appetite. Under these circumstances small amounts of beverages containing 5 to 10 per cent. of alcohol are sufficient for all purposes.[1]

In the light of the social evils which accompany the excessive use of alcohol as a beverage there is no doubt that its total prohibition—if this were possible—would make for the public weal and improve the physical and moral condition of mankind.

The subject of alcohol could be spun out into a considerable story, but for further details the reader is referred to other sources.[2]

The ash constituents of a dietary are certainly of importance.[3] In fasting there is a constant loss of salts from the body. There is apparently a "wear-and-tear" metabolism of the bones (see p. 99) which must be replaced by ingested salts.

The minimum amount of calcium needed in the daily diet in order to establish "calcium equilibrium" is unknown. Benedict's fasting man eliminated 0.138 gram of calcium oxid in the urine of the thirty-first day of his fast.

From the work of Bertram,[4] it appears that a man can be maintained in calcium equilibrium when the diet contains 0.4 gram of calcium oxid. Herxheimer[5] obtained the same result when a man took 0.86 gram of calcium oxid.

German authorities state that a man requires about 1.5 grams of calcium oxid daily. Thus Hornemann[6] places the

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[1] Zitowitsch: Abstract in "Biochem. Centralblatt," 1905, iv, 574.

[2] "The Use of Alcohol in Medicine": F. G. Benedict, A. R. Cushny, S. J. Meltzer, Graham Lusk, "Boston Medical and Surgical Journal," 1902, cxlvii, 31; "Bibliographie der gesammten wissenschaftlichen Literatur über den Alkohol und den Alkoholismus," 1904, by Emil Abderhalden.

[3] For the older literature see Albu and Neuberg: "Physiologie und Pathologie des Mineralstoffwechsels," 1906.

[4] Bertram: "Zeitschrift für Biologie," 1878, xiv, 354.

[5] Herxheimer: "Berliner klinische Wochenschrift," 1897, xxxiv, 423.

[6] Hornemann: "Zeitschrift für Hygiene," 1913, lxxv, 553.

requirement of calcium oxid at 1.7 grams and of iron at 55 milligrams, the sodium chlorid balance being maintained with 5 grams of that salt daily, or half to one-quarter the amount usually taken.

Tigerstedt[1] reports that the diet of the Finns contains between 2 and 6 grams of calcium oxid daily, and this on account of the large intake of milk (see p. 348), which averages 1570 c.c. for men and 913 c.c. for women.

In contrast with this, the ordinary American diet of the average inhabitant of the Eastern States, as studied by Sherman, Mettler, and Sinclair[2] presents a sorry spectacle.

The salt content of the dietaries taken by the people of the two nations may be thus contrasted:

ASH CONTENT OF ORDINARY DIETARIES, WEIGHTS IN GRAMS

Calories in Diet.	Finnish.			American.		
	P_2O_5.	Ca.O.	Mg.O.	P_2O_5.	Ca.O.	Mg.O.
Over 4000...	10.86	6.10	2.02	4.24	0.79	0.89
4000–3500...	9.46	3.79	1.85	3.22	0.94	0.51
3500–3000...	8.18	4.02	1.53	3.29	0.99	0.50
3000–2500...	6.93	3.51	1.23	3.20	0.92	0.46
2500–2000...	5.64	2.96	1.03	2.06	0.36	0.32
2000–1500...	5.12	2.85	0.78	1.84	0.68	0.23

Tigerstedt points out that this difference in the salt intake of the different peoples is due to the fact that the American subjects took an average of only 250 c.c. of milk in their diets daily. As pointed out by Sherman, the American family has only to drink more milk or eat more cheese in order to raise the ash content of the dietary. Those in charge of the food supply of institutions should not forget the importance of milk, and every care should be exercised to prevent the cost of good milk from becoming prohibitive.

[1] Tigerstedt, R.: "Skan. Archiv für Physiologie," 1911, xxiv, 97.

[2] Sherman, Mettler, and Sinclair: U. S. Dept. of Agriculture, Office of Experiment Stations, 1910, Bulletin No. 227 A. Table giving the ash constituents of the edible portions of various food materials is given in this bulletin on p. 41.

The American families were reported to consume between 35 and 7 milligrams of iron daily, the amount ingested running almost parallel with the intake of protein in the food. This is much less than the minimum called for by Horneman.

The question of the minimal quantity of ash intake for human beings is far from settled.

The following table, compiled from part of the data presented by Sherman[1] and by Sherman and Gettler,[2] gives the ash content of various edible foods:

ASH CONTENT OF THE EDIBLE PORTION OF SOME COMMON FOODS

	In 100 Grams Fresh Substance.						
	Iron.	Calcium.	Magnesium.	Sodium.	Potassium.	Phosphorus.	Chlorin.
	Mg.	Mg.	Mg.	Mg.	Mg.	Mg.	Mg.
Beefsteak, lean	3.8	8	24	67	35	22	50
Eggs	3.0	67	9	15	14	16	100
Milk, whole	0.2	120	11	51	142	94	120
Cornmeal	1.1						
Oatmeal	3.7	93	127	81	380	380	35
Rice, polished	0.7	8	27	21	68	89	50
Wheat flour	1.5	26	30	69	146	86	76
Wheat, entire grain	5.2	44	170	106	515	469	88
Beans, lima, dried	7.2	71	187	245	1743	336	25
Beans, string, fresh	1.6						
Cabbage	0.9	49	14	20	243	27	13
Corn, sweet	0.8						
Peas, dried	5.6	100	145	118	880	397	40
Potatoes	1.2	11	22	19	440	61	30
Spinach	3.8						
Turnips	0.6	64	169	59	332	51	40
Apples	0.3	10	8	15	125	13	4
Raisins	3.6	57	9	141	830	126	70

Meat, eggs, oatmeal, unmilled wheat, and green vegetables contain much iron. Milk, polished rice, and white flour contain little iron. Milk, oatmeal, and dried beans furnish large amounts of calcium.

Not only is the quantity of the ash constituents of signif-

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[1] Sherman: "The Chemistry of Food and Nutrition," New York, 1911.

[2] Sherman and Gettler: "Journal of Biological Chemistry," 1911–12, xi, 323.

icance, but Sherman and Gettler[1] have shown the importance of the acid or base-forming potency of the ash of different foods. Thus, a dietary which contained 3000 calories, 300 calories being in potato, was given to a man, and then the potato was replaced by rice containing 300 calories. The result of the change was an increase of 50 per cent. in the titratible acidity of the urine and an increase in the amount of ammonia excreted.

Blatherwick[2] has continued investigations along these lines, which show that foods which have a preponderance of base-forming elements lead to the formation of a urine less acid than the normal. Such foods are potatoes, oranges, raisins, apples, and bananas, and these are very efficient in reducing the acid output. Tomatoes are less valuable in this respect. Rice and whole wheat bread increase urinary acidity. Plums, prunes, and cranberries, through their content of benzoic acid, increase the urinary acidity. Blatherwick notes that the hydrogen ion concentration of thirty urines obtained from vegetarians was -6.64, in contrast with a value of -5.98 reported by Henderson and Palmer for the urines of persons living on a mixed diet, and he emphasizes the close relationship between the hydrogen ion concentration of the urine and its solvent power over uric acid. These findings are, therefore, in accord with those of Hindhede (p. 341) and should establish the potato upon a high plane of dietary dignity.

To arrange a proper dietary for a given individual or group of individuals the very complete and valuable tables of Atwater will be found most practical. They are placed in an appendix at the end of this volume for the benefit of the student who may desire to apply in practice his knowledge of the general laws of metabolism.

Underfed or overfed individuals may alike become objects of commiseration and proper subjects for rehabilitation.

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[1] Sherman and Gettler: *Loc. cit.*

[2] Blatherwick: "Archives of Internal Medicine," 1914, xiv, 409.

CHAPTER XIII

THE NUTRITIVE VALUE OF VARIOUS MATERIALS USED AS FOODS

In 1897 Eijkman[1] published the observation that the disease beriberi was due to a one-sided diet of polished rice, and that if rice were not milled, but eaten with its pericarp, beriberi did not ensue. Eijkman[2] also made the very valuable discovery that pigeons, when fed with polished rice, developed a polyneuritis analogous to that found in human beriberi, and that the addition of rice bran (rice polishings) to the diet prevented this condition.[3]

About this same time Röhmann[4] found that if, instead of natural foods, purified materials, such as casein, egg-albumin, vitellin, potato starch, wheat starch, and oleomargarin, together with the proper salts, were mixed and given to mice, their offspring were difficult to rear with this food and that no living young could be obtained from them.[5] These experiments appeared difficult of interpretation.

In reality, the work of Eijkman and of Röhmann was the beginning of a scientific knowledge of the so-called "deficiency diseases." It now appears that a proper diet for growth or maintenance must contain not only protein, fat, carbohydrate, and salts, but also some substances existing in natural foods, in very minute quantities, which are absolutely essential to the harmonious fulfilment of the life processes. It should be added that Röhmann denies the necessity of these accessory substances.

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[1] Eijkman: "Virchow's Archiv," 1897, cxlix, 187.

[2] Eijkman: *Ibid.*, 1897, cxlviii, 523.

[3] For useful reference consult Vedder, E. B.: "Beriberi," New York, 1913.

[4] Röhmann: "Klinische therapeutische Wochenschrift," 1902, No. 40.

[5] Consult Osborne and Mendel: Carnegie Institution, Publication 156, 1911; Röhmann: "Ueber künstliche Ernährung und Vitamine," Berlin, 1916.

Another pioneer in this field was Gowland Hopkins,[1] who wrote in 1906, "No animal can live on a mixture of pure protein, fat, and carbohydrate, and even when the necessary inorganic material is carefully supplied the animal still cannot flourish. The animal is adjusted to live either on plant tissues or the tissues of other animals, and these contain countless substances other than proteins, carbohydrates, and fats. . . . In diseases such as rickets and, particularly, in scurvy we have had for long years knowledge of a dietetic factor; but though we know how to benefit these conditions empirically, the scale errors in the diet are to this day quite obscure. . . . Scurvy and rickets are conditions so severe that they force themselves on our attention; but many other nutritive errors affect the health of individuals to a degree most important to themselves, and some of them depend upon unsuspected dietetic factors."

The study of the "accessory factors" of diet, a term used by Hopkins, has been in the hands and heads of some of the ablest physiologic chemists during the past ten years, and it is extremely difficult, perhaps impossible, to write of the subject and do even-handed justice toward the various contributors in the field. Hofmeister defines the unknown but beneficent factors alluded to here as "accessory food-stuffs," and Funk has called them "vitamins."[2] Objection is made to the term "accessory" on the ground that it implies something non-essential, and to the term "vitamin" on the ground that there is no evidence that the substance or substances in question are amins, nor that they are more valuable to life than other substances—epinephrin, for example. In acknowledgment of this insufficiency of information, McCollum[3] suggests the provisional use of two terms, the "fat-soluble A" and the "water-soluble B," as representing the factors necessary for adequate growth. The "water-soluble

[1] Hopkins, F. G.: "Analyst," 1906, xxxi, 391.

[2] Funk: "Ergebnisse der Physiologie," 1913, xiii, 126.

[3] McCollum, E. V.: "Journal of Biological Chemistry," 1916, xxv, 105.

B" cures beriberi and is regarded as identical with Funk's "vitamins."

For the sake of simplicity, the word "vitamin" may be retained provisionally to express the group of as yet unidentified substances which cannot at present be classified with the familiar nutrients, proteins, fats, carbohydrates, inorganic salts, and water, upon which the harmonious behavior of the organism depends and which are ordinarily ingested in traces in the food. The term "food hormone" is probably a more rational expression of what the vitamins signify (see p. 378).

Interwoven with the experimental work upon the subject of the vitamins has been work upon the relative value of different proteins in nutrition. A diet may yield sufficient energy to maintain the organism and yet be a deficient dietary in that it lacks vitamins or contains insufficient salts or too little protein or protein of low nutritive value.

Stepp[1] showed that when mice were fed with bread baked with a little milk this formed a complete diet, but if this diet were first extracted with alcohol and ether the animals all died. He[2] further reported that the addition of salts or fat or lecithin or cholesterol to the extracted bread was without beneficial influence when it was given to mice. However, the addition of ether-alcohol extracts from skimmed milk, from egg-yolk, or from calf's brains to bread which had been extracted furnished a diet capable of supporting mice. In a later paper Stepp[3] reported that ether extraction fails to remove the accessory substance necessary to life, whereas alcohol accomplishes this result; he therefore concludes that the significant substance is not a fat.

In 1912 Holst and Frölich[4] reported that if guinea-pigs were fed with a one-sided diet of white bread, or with polished rice or other milled grains, they invariably died, usually in about four weeks. They always showed loose teeth and

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[1] Stepp, W.: "Biochemische Zeitschrift," 1909, xxii, 452.

[2] Stepp, W.: "Zeitschrift für Biologie," 1911–12, lvii, 135.

[3] Stepp, W.: *Ibid.*, 1913, lxii, 405.

[4] Holst and Frölich: "Zeitschrift für Hygiene," 1912, lxxii, 1.

usually hyperemic gums. Hemorrhages appeared, sometimes in the skin, but more usually at the knee-joints and at the cartilages of the ribs, and there were microscopic changes in the bone-marrow. All these phenomena are in entire accord with the manifestations of human scurvy. It is important to remember that it has never been demonstrated that any kind of unmilled grain will produce scurvy. Materials in the pericarp are, therefore, essential to health. As antidotes to foods which produce scurvy, fresh vegetables, dried peas, lime-juice, or fermented liquors (wines, beer) are antiscorbutic and cure human scurvy as well as the form artificially induced in animals. Drying or heating some of the effective substances to 110° reduces the antiscorbutic effect.

Hess[1] reports that in an asylum where infants were fed with pasteurized milk during a period of four months scurvy developed, accompanied by a stunting in the normal growth of the infants. This was at once corrected by the administration of orange-juice.

Lime-juice was early found to be a preventive of scurvy, and its introduction into the British Navy in 1795 led to the disappearance of the disease among the sailors.

Holst[2] describes how Cartier on his second voyage to Newfoundland, in 1535, administered with great success a fresh decoction of pine needles to a crew of 103 men of whom only 3 were free from scurvy. When the Eskimos suffer from this disease Holst states that they turn to the liver of seals or, better, to fresh "matok," which is the rete Malpighii of the skin of whales.

During the siege of Paris scurvy broke out on a large scale on account of the prolonged one-sided diet of farinaceous nutriment. Under ordinary conditions in civilized communities scurvy is of rare occurrence, although it has been known

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[1] Hess, A. F.: "Proceedings of the Society for Experimental Biology and Medicine," 1915, xiii, 50.

[2] Holst: "XVth International Congress of Hygiene," Washington, 1912, ii, 588.

to develop in poorhouses which have been placed under ignorant or dishonest control.

Another disease which, in all probability, is a deficiency disease, is pellagra. Funk[1] states that in the United States between 1907 and 1912 20,000 persons died of pellagra, the mortality being 40 per cent. among those suffering from the disease. Pellagra occurs in the "corn belt" of the United States, and especially among the poorer classes of the South. The disease has developed since the introduction in 1880 of highly perfected machinery which furnishes corn and wheat completely freed of their outer coverings. In Italy, where the process of milling corn is primitive, the mortality among the pellagrins is only 4 per cent. Nightingale[2] reports that in a prison in Rhodesia, where hand-milled maize was given, this food proved to be adequate, but when maize without its skin was substituted 1210 cases of pellagra occurred. There is no pellagra in zones where the potato is cultivated. Nightingale concluded that the disease was in no way infectious or contagious. Green vegetables, meat, butter, and potatoes are found to be the best antidotes.

Goldberger[3] reports that at an isolated convict camp in Mississippi 11 volunteers were placed on a one-sided diet of wheat, corn, and rice, as the result of which 6 individuals developed pellagra after the diet had been administered for about five months.

Vedder[4] believes that pellagra, like beriberi and scurvy, is a deficiency disease, though the possibility of its being of infectious nature remains an open question. The deficiency is attributed to a too exclusive use of wheat flour in association with cornmeal, salt meats, canned goods, all of which are deficient in vitamins. He writes: "If pellagra is a deficiency disease it has an extremely long depletion period. If Gold-

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[1] Funk: "Münchener medizinische Wochenschrift," 1914, lxi, 698.

[2] Nightingale: "British Medical Journal," 1914, No. 1, 300.

[3] Goldberger: "Journal of the American Medical Association," 1916, lxvi, 471.

[4] Vedder, E. B.: "Archives of Internal Medicine," 1916, xviii, 137; "Journal of the Amer. Med. Assoc.," 1916, lxvii, 1494.

berger and his associates produced pellagra in their human feeding experiments, the depletion periods on the diets used may be placed at at least five months."

The United States Public Health Service has maintained an important station at Spartanburg, S. C., in the heart of the pellagra district, and has issued several valuable reports which cannot here be detailed.[1]

One may now pass to the more detailed consideration of the vitamins, the acknowledged discoverer of which is Gowland Hopkins. An important advance was scored when Funk[2] separated a material from yeast a few milligrams of which cured polyneuritis in pigeons. From 100 kilograms of dry yeast he[3] extracted 2.5 grams of a material which, when administered in doses of 2 milligrams to pigeons paralyzed with beriberi induced by a diet of polished rice, cured them in three hours.

Working in Japan, Suzuki, Shimamura, and Odake[4] extracted rice-bran first with ether and then with alcohol. The purified substance obtained from the alcohol extract was said to cure beriberi in pigeons when 10 milligrams of the material were administered.

The effect of the vitamins upon growth has been especially studied by Osborne and Mendel and by McCollum and Davis. Whether there are specific vitamins for growth has not been clearly established.

Experiments concerning growth may be conducted with especial ease upon pigs and rats. McCollum[5] concludes that the growth impulse of the pig is greater than that of the rat on account of the data contained in the following table:

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[1] Hunter, Givens, and Lewis: "Preliminary Observations of Metabolism in Pellagra," Hygienic Laboratory, Bulletin 102, 1916; Koch and Voegtlin, "Chemical Changes in the Central Nervous System as a Result of Restricted Vegetable Diet," Hygienic Laboratory, Bulletin 103, 1916.

[2] Funk: "Journal of Physiology," 1911–12, xliii, 395.

[3] Funk: *Ibid.*, 1913, xlvi, 173; *ibid.*, 1914, xlviii, 228.

[4] Suzuki, Shimamura, and Odake: "Biochemische Zeitschrift," 1912, xliii, 89.

[5] McCollum: "Journal of Biological Chemistry," 1914, xix, 323.

	At Birth.		Age = 280 Days.		Weight at 280 Days / Weight at Birth.	
	Weight, Grams.	Body N, Grams.	Weight, Grams.	Body N, Grams.	Body Weight.	Body N.
Rat	4.83	0.064	280	8.5	55	133
Pig	906.	11.9	136,000	2407.	150	202

It is evident that the pig, both as regards body weight and nitrogen content, increases relatively somewhat more rapidly than does the rat. However, in both species the growth impulse is very great and very constant, so that deviations in the curve of normal growth, when caused by insufficiency of diet, may be readily established. The rat reaches full growth after two hundred and eighty days and lives about three years.

In 1911 Osborne and Mendel[1] published the first results of a prolonged series of valuable contributions to the knowledge of growth. These authors found that if a single protein, like casein, were added to a diet made up of starch, lard, agar, and "protein-free milk," such a diet became adequate for the growth of rats during the first two months of their lives. This is because it contains "water-soluble" vitamins. The "protein-free milk" contains 0.7 per cent. of nitrogen, 80 per cent. of lactose, and 15 per cent. of inorganic salts, and Osborne and Mendel[2] estimate that 2.2 per cent. of milk protein is present. This makes 0.6 per cent. of the weight of the whole diet, or 3 per cent. of the total quantity of protein ingested when an isolated protein, like casein, is added to the food in such measure as to make the diet contain 18 per cent. of casein. In later work Osborne and Mendel state that the "protein-free milk" introduces protein only to the extent of 0.13 per cent. of the food given.

Hopkins[3] showed that a synthetic food, consisting of protein, carbohydrate, lard, and the proper salts, became an

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[1] Osborne and Mendel: "Feeding Experiments with Isolated Food-substances, Parts I and II," Carnegie Institution, 1911, Publication 156.

[2] Osborne and Mendel: "Zeitschrift für physiologische Chemie," 1912, lxxx, 316.

[3] Hopkins, F. G.: "Journal of Physiology," 1912, xliv, 425.

entirely satisfactory diet for growing rats if only 2 c.c. of milk were given also. The milk was administered before the rest of the diet in order to prove that it was not a lack of palatability in the synthetic food which was the cause of the failure of the rats to grow. Hopkins also made the very significant discovery that an alcoholic extract of milk solids or of yeast, when added to the synthetic diet "in astonishingly small amounts," caused normal growth. Though the synthetic diet contained plenty of calories (see p. 414) growth took place only when the accessory substances were administered.

McCollum and Davis[1] reported that, although young rats grew for sixty or ninety days on such diets as have been described, yet after this time growth suddenly stopped. It could be re-established if butter fat or the ether extract of egg-yolk was added to the diet. Apparently, the organism runs out of some organic complex which is indispensible to normal growth and without which maintenance in good condition is impossible.

Osborne and Mendel[2] independently reached the same results. There was a primary growth when a synthetic diet which included lard and "protein-free milk" was given, followed by failure to grow. If the lard were replaced by butter or egg-yolk or cod-liver oil, growth was resumed, but almond oil was inefficient in this regard. In connection with the high efficacy of cod-liver oil in promoting growth, Osborne and Mendel refer to its "popular yet inexplicable reputation for unique nutritive potency." Beef fat was found to be more valuable than lard.

McCollum and Davis[3] show that olive oil and cotton-seed oil, like almond oil and lard, cannot be used to foster growth, whereas the fat of cod testicle and pig's kidney are very efficient. Curiously enough, the fat of the pig's heart is not of value in producing growth. Animal fats and especially

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[1] McCollum and Davis: "Journal of Biological Chemistry," 1913, xv, 167.

[2] Osborne and Mendel: *Loc. cit.*, 1913, xv, 311; xvi, 423; 1914, xvii, 401.

[3] McCollum and Davis: *Loc. cit.*, 1914, xix, 245; 1915, xx, 641; xxi, 179.

milk fats have, therefore, nutrient virtues not expressed in calories.

McCollum and Davis[1] have given to rats a standard diet without any fat in it and have brought them after twenty to twenty-five weeks to the threshold of death. Then on giving the standard diet with an equal quantity of different grains the following results were observed:

Cornmeal,	Surprising recovery and growth.
Wheat embryo,	Recovery and growth.
Entire wheat kernel,	Recovery, no growth.
Rye,	Little or no improvement.
Oats,	Little or no improvement.

The authors remark that such results illustrate the paucity of our knowledge regarding the special nutritive value of the common cereals.

Finally McCollum and Davis[2] describe how, if casein be dialyzed against water and acetic acid so that all the salts are washed out, this product when given with butter, dextrin, and salts causes no growth in rats.

For a more complete discussion the reader is referred to other sources.[3] One may, however, summarize the work upon the influence which the ingestion of purified food-stuffs has upon growth, as follows:

Purified protein + carbohydrate + vegetable fat + inorganic salts = no growth.
Purified protein + carbohydrate + butter fat + inorganic salts = no growth.
Purified protein + carbohydrate + vegetable fat + inorganic salts + vitamins* = no growth.
Purified protein + carbohydrate + butter fat + inorganic salts + vitamins* = growth.

* Water or alcohol extract of peas, rice polishings, wheat, yeast, or "protein-free milk," which are able to cure polyneuritis in a pigeon in a few hours.

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[1] McCollum and Davis: "Journal of Biological Chemistry," 1915, xxi, 179.

[2] McCollum and Davis: *Ibid.*, 1915, xxiii, 231.

[3] Mendel: "Journal of the American Medical Association," 1915, lxiv, 1539; McCollum: "New York Medical Journal," 1916, ciii, 838.

The value of the water-soluble and the fat-soluble vitamins is apparent.

Since the purified protein may be given free from phosphorus without prejudice to the capacity to grow, it is evident that an animal, when fed with a diet of pure protein, carbohydrate, fat, and simple inorganic salts, may produce synthetically lecithin, phosphatids, nuclear material (purins, etc.), hemoglobin, and bone-tissue. McCollum states that he has never seen growth enhanced by the addition of organic phosphorus to a diet. Certain amino-acids, however, must be furnished preformed. Mendel and Osborne and McCollum and Davis are in essential accord with regard to these underlying principles, and science owes them much for their laborious and painstaking contributions to this long obscure chapter of dietetics.

In another chapter of this book (see p. 156) the unequal nutritional value of the proteins, such as are found in meat or gelatin, have been emphasized. This difference in nutritive value was set forth by Karl Thomas,[1] who took starch and sugar in large quantity in his diet, determined the minimal loss of body protein under these circumstances, and then added to the diet food materials containing different proteins, in order to determine their relative power in sparing the body from a loss of tissue protein. The values given below Thomas named the *biologic values* of the proteins employed:

BIOLOGIC VALUES OF DIFFERENT PROTEINS, AS MEASURED BY THE PERCENTAGE QUANTITY OF BODY PROTEIN WHICH THEIR INGESTION WILL SPARE FROM LOSS

Ox meat	104	Cherry-juice	79
Cows' milk	100	Yeast	71
Fish	95	Casein	70
Rice	88	Nutrose	69
Cauliflower	84	Spinach	64
Crab meat	79	Peas	56
Potatoes	79	Wheat flour	40
		Cornmeal	30

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[1] Thomas, K.: "Archiv für Physiologie," 1909, p. 219.

These excellent experiments show clearly the superior value of meat, fish, and milk proteins as conservers of body protein when contrasted with the ordinary group of vegetable proteins.

The reason for this biologic difference lies in the amino-acid content of the different proteins, as has been beautifully shown in experiments with growing animals. Willcock and Hopkins[1] were the pioneers in this field. They prepared a diet in which *casein* was the sole nitrogenous constituent and obtained good growth in mice when this diet was administered to them. When *zein*, the principal protein of corn, was substituted for casein in the diet, the animals declined and died in about seventeen days. Addition of tyrosin, which zein contains in plentiful amount, was without effect upon the length of life. When, however, tryptophan, which, as well as lysin and glycocoll, is absent from the zein molecule, was added to the diet in an amount equal to 2 per cent. of the total zein given, the animals lived thirty-two days. Hopkins suggests the possibility that in the absence of tryptophan epinephrin cannot be formed and collapse follows. Osborne and Mendel[2] have maintained a rat at an almost constant body weight of 50 grams for one hundred and eighty-two days on a food containing zein as its dominant protein, with the addition of tryptophan equal to 3 per cent. of the zein. Since zein is free from the amino-acid lysin, it seemed possible that normal growth might be obtained when the protein in the dietary consisted of zein supplemented by tryptophan and lysin; such, indeed, proved to be the case (Fig. 22).

A striking detail of this work is that at the beginning of the experiment a patch of hair on the animal's back was dyed red and this color remained unchanged for six months. When lysin was added to the diet and growth was resumed the color soon disappeared. New growth became possible in the hairs

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[1] Willcock and Hopkins: "Journal of Physiology," 1906–7, xxxv, 88.

[2] Osborne and Mendel: "Journal of Biological Chemistry," 1915, xx, 351.

as in other parts of the body. The addition of lysin alone to a dietary containing zein does not prevent the decline which always accompanies the partaking of a diet which is free from tryptophan.

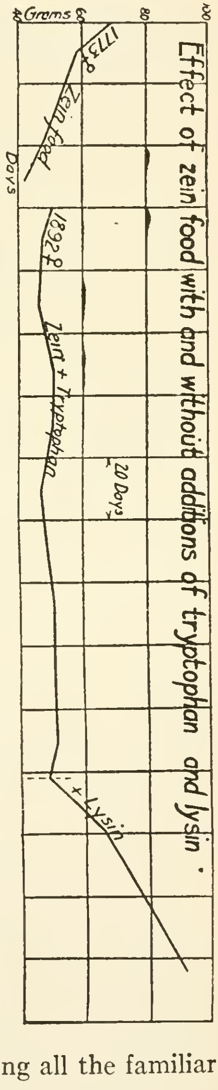

Fig. 22.—Showing *nutritive decline* on zein food, *maintenance* after addition of tryptophan, *growth* after addition of both tryptophan and lysin. Rat 1892 was maintained during one-half year without significant change in body weight on the zein + tryptophan food. Despite this inadequate diet the capacity to grow was not lost at the end of this prolonged period, and the animal ultimately grew to full adult size on a mixed diet.

From the experiments of McCollum,[1] one may calculate that gelatin (which lacks tyrosin, tryptophan, and cystin) when given with starch to a pig in such quantity that the gelatin is the equivalent of the "wear-and-tear" quota of protein metabolism body protein is protected from waste to an extent of 39 per cent. (see p. 283). When zein is administered under similar conditions body protein is spared to an extent of 73 per cent., thus demonstrating the superiority of zein to gelatin in this regard.

The study of the failure of zein to produce growth or to prevent decline brings up the question as to the nutritive value of maize. Osborne and Mendel[2] state that zein and glutelin form 72 per cent. of the proteins of the maize kernel. Glutelin, which is present in about one-half the quantity of that of zein, is a complete protein, containing all the familiar

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[1] McCollum, E. V.: "American Journal of Physiology," 1911–12, xxix, 215.

[2] Osborne and Mendel: "Journal of Biological Chemistry," 1914, xviii, 1.

amino-acids, and is efficient in producing growth, but there is not enough of this higher quality protein to produce more than moderate growth. A small addition of a protein like lactalbumin, however, to a diet containing maize protein at once induced normal growth.

The corn grain contains little calcium, and the daily addition of 2.5 grams to the diet of a corn-fed pregnant sow very favorably influences the condition of the offspring.[1]

Hart and McCollum[2] noticed that when swine are restricted to cornmeal and corn-gluten feed there is little or no growth, but when salts are added, so that the salt content of the ration approximates that of milk, good growth follows. The desire for salts may explain the "rooting" of the hog. The desirability of a milk addition to the diet of the growing hog is emphasized in the following experiment, which shows the higher biologic value of the milk proteins as contrasted with vegetable proteins. (See also p. 371.)

EFFECT OF THE KIND OF PROTEIN UPON THE AMOUNT OF PROTEIN RETAINED FOR GROWTH

Source of Protein.	Calories Per Kg. in Ration.	Protein in Per Cent. in Ration.	Protein Retained for Growth in Per Cent.
Corn	109	10.5	20
Wheat	103	11.0	22
Oats	94	14.5	23
⅓ corn + ⅓ wheat + ⅓ oats	98	12.3	26
Wheat embryo + wheat gluten	98	57.9	21
Casein	102	16.5	46
Skim milk	94	15.5	63

When vegetable protein was administered in large quantity there was about the same percentage retention as when it was given in smaller amount. Hence, McCollum concludes that the limitation of growth when vegetable proteins

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[1] Evvard, Dox, and Guernsey: "American Journal of Physiology," 1914, xxxiv, 312.

[2] Hart and McCollum: "Journal of Biological Chemistry," 1914, xix, 373. Consult also Hogan: *Ibid.*, 1916, xxvii, 193.

are taken alone is due to the chemical make-up of these proteins and not to any diminution in the animal's power to grow.

The work of Osborne and Mendel upon the subject of the behavior of *gliadin*, one of the principal proteins derived from *wheat*, has been of very great interest. Gliadin is a protein which yields 44 per cent. of glutamic acid and 13 per cent. of prolin, these being present in exceptionally large quantities. On the other hand, it contains only 0.92 per cent. of lysin and very little arginin and histidin. When gliadin is the only protein in the diet grown rats may be maintained over long periods (546 days), but ungrown rats fail to grow,[1] although the gliadin administered is completely digested and absorbed. The animals remain stunted and resume growth only when an adequate protein in the diet is offered to them. Osborne and Mendel[2] have stunted albino rats until they were 550 days old, and then by a change of diet observed a resumption and completion of growth, although ordinarily such completion of growth is accomplished before the age of 300 days. It appears that if in these animals the function of growth has not been fulfilled at the usual period of life the capacity to grow is never lost.

If a diet be made up which contains gliadin as the dominant protein, and lysin be added so that the protein quota contains 2 or 3 per cent. of lysin, normal growth is resumed by a rat which had been stunted through the influence of the diet poor in lysin.[3]

The principal proteins existing in wheat are gliadin and wheat *glutenin*, there being equal amounts of each. Since the latter form of protein completely suffices for the growth of rats, it is evident that the value of wheat protein is greatly enhanced by the presence of this constituent.

A notable contribution to the knowledge of the relative value of lactalbumin and casein has been presented by

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[1] Osborne and Mendel: "Journal of Biological Chemistry," 1912, xii, 473.
[2] Osborne and Mendel: *Ibid.*, 1915, xxiii, 439.
[3] Osborne and Mendel: *Ibid.*, 1916, xxv, 1.

Osborne and Mendel.[1] It will be remembered that Thomas found that casein was inferior to milk protein for the maintenance of nitrogen equilibrium in man. The cause of the

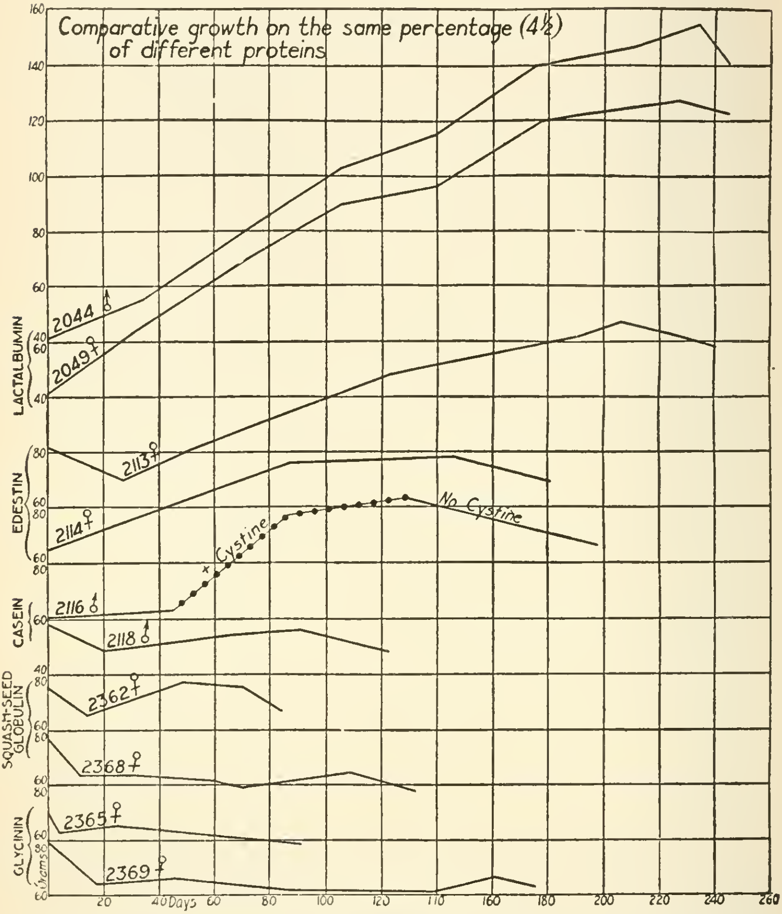

Fig. 23.—Comparison of growth on diets containing approximately the same percentage (4.5 per cent.) of different proteins, namely, *lactalbumin*, *edestin*, *casein*, *globulin* (squash-seed), and *glycinin* (soy bean).

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[1] Osborne and Mendel: "Journal of Biological Chemistry," 1915, xx, 351; 1916, xxvi, 1.

inferiority of casein is largely due to the fact that it contains only 0.6 per cent. of cystin (Fig. 23).

When 3 per cent. of this latter amino-acid is added to the casein content of a diet, Mendel and Osborne found that growth in the rat was accomplished with a much smaller quantity of protein than when casein alone was given. These results are presented in the following table:

INFLUENCE OF THE AMOUNT OF DIFFERENT VARIETIES OF MILK PROTEIN UPON THE GROWTH OF RATS

Percentage of Protein in the Diet.	Casein.	Casein + 3 Per Cent. Cystein.	Lactalbumin.
18	Normal.		Normal.
15	Normal.		Normal.
12	Little below normal.		Normal.
9	Limited.	Normal.	Normal.
6	Slight.	Good.	
4½	Maintenance.	Slight.	Limited.
2	Decline.		Maintenance.
1			Decline.

It is evident that a diet containing 15 per cent. of casein may be given to rats and produce normal growth, whereas when 12 per cent. is present normal growth does not take place. The addition of 3 per cent. of cystein to casein so that this mixture forms 9 per cent. of the diet yields a food capable of supporting normal growth. There is greater value in lactalbumin in promoting growth than in casein because the amino-acids are arranged in more suitable proportions. The protein of whey appears to be as perfect a material for use in the service of growth as any protein known.

The following table, which is arranged from data given by Mendel,[1] presents the proteins with a supply of which an organism may grow, and also those which, if fed, do not produce growth of the organism:

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[1] Mendel: Harvey Society Lecture, "Journal of the American Medical Association," 1915, lxiv, 1539.

VALUE OF PROTEINS IN THE FUNCTION OF GROWTH

Allow Growth.		Failure to Grow.	
Casein	milk.	Legumelin	soy bean.
Lactalbumin	milk.	Vignin	vetch.
Ovalbumin	hen's egg.	Gliadin	wheat or rye.
Ovovitellin	hen's egg.	Legumin	pea.
Edestin	hemp-seed.	Legumin	vetch.
Globulin	squash-seed.	Hordein	barley.
Excelsin	Brazil-nut.	Conglutin	lupin.
Glutelin	maize.	Gelatin	horn.
Globulin	cotton-seed.	Zein	maize.
Glutenin	wheat.	Phaseolin	white kidney bean.
Glycinin	soy bean.		
Cannabin	hemp-seed.		

It is evident from the material presented in this chapter that the science of nutrition includes something more than the production of energy from fat, carbohydrate, and protein. There must be certain salts and certain qualities of protein in the diet, and there must be minute amounts of "vitamins." The chemical composition of the latter will some day be known,[1] even as the chemical composition of epinephrin is known. Epinephrin, an essential of life, is present in the blood to the extent of 1 part in 100,000,000. In like manner, vitamins which are present in meat, milk, fresh green vegetables, and grains are essential to the harmonious correlation of the nutritive functions of animals. Lafayette Mendel first suggested the use of the word "hormone" in connection with the vitamins. Gowland Hopkins adopts the term "exogenous hormones." The expression "food hormones" would also be exactly descriptive of the nature of these substances.

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[1] Williams and Seidell ("Journal of Biological Chemistry," 1916, xxvi, 431) have separated from the filtrate of autolyzed yeast a crystalline antineuritic substance which, on recrystallization, lost its antineuritic properties and was converted into adenin. The authors suggest that an isomer of adenin is the chemical entity responsible for the physiologic properties of the vitamin of yeast. They are continuing this inquiry.

CHAPTER XIV

THE FOOD REQUIREMENT DURING THE PERIOD OF GROWTH

"MUTE and still, by night and by day, labor goes on in the workshops of life. Here an animal grows, there a plant. The wonder of the work is not less in the smallest being than in the largest."[1]

In the last chapter the average food requirement of a normal adult organism was discussed. This diet, however, may be exceeded in cases where there is a renewal of tissue following wasting disease, or where there is a development of new tissue, as during pregnancy, or afterward during lactation, which involves the growth of the newborn infant.

Tangl[2] has reported some interesting observations on the heat production which takes place in the hen's egg incubated at 38° and 39° F. Tangl called this the "energy for development" or the "ontogenetic energy." His method was to determine the calories in fresh laid eggs and to compare that amount with the calories found within the egg-shell at the moment of the birth of the chick. In this latter case the chick and the balance of egg-yolk were determined separately.

The results of these experiments showed that for the development of 1 gram of chick 658 small calories were used, or for the production of 1 gram of solids contained in a newborn chick 3425 small calories were required.

Farkas[3] has since shown that for the development from the egg of 1 gram of silkworm larvæ 882 small calories are required, or for 1 gram of dry solids, 3125 small calories, figures which he compares with Tangl's for the egg.

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[1] Rubner: "Verhandlungen der Ges. der Naturforscher und Ärzte," 1908, p. 77.

[2] Tangl: "Pflüger's Archiv," 1903, xciii, 327.

[3] Farkas: *Ibid.*, 1903, xcviii, 490.

When the whole hen's egg is considered, Tangl finds that 32 calories or 35 per cent. of the amount of chemical energy in the original egg is deposited in the body of the young embryo. The energy of development used in the production of the young chick amounts to 16 calories or 17 per cent. of the original total. The balance, 44 calories or 48 per cent. of the original energy in the egg, is largely found in the abdomen of the chick and is absorbed by the animal during the early days of life.

It is apparent from the above that approximately one-sixth of the energy in a hen's egg is used in the development of a chick whose body contains one-third the original energy of the egg. The other half of the energy becomes available for the chick during the first days of its separate life through absorption from the intestinal wall.

Tangl finds that each egg loses in solids during incubation, and that the heat value of 1 gram of such solids is over 9 calories. Since 1 gram of fat yields 9.3 calories, the natural inference is that fat furnishes the energy for development.

Hasselbalch[1] had formerly shown that the respiration carried on by an egg indicated a respiratory quotient amounting to 0.677. This low quotient points to the combustion of fat.

Tangl[2] also states that there is no loss of protein nitrogen by the egg during incubation, and that the egg-shell contributes to bone formation in the chick.

Glaser[3] has found that the energy of ontogenesis for the eggs of fundulus is similar in quantity to that necessary for the hen's egg and for silkworm larvæ, and is also evolved at the expense of the oxidation of fat. He reiterates Tangl's statement that the specific energy of ontogenesis is not a function of phylogenetic position or of organization, but that the embryonic construction of different kinds of highly organized living forms may take place at the same expense of chemical energy.

[1] Hasselbalch: "Skan. Archiv für Physiol.," 1900, x, 353.

[2] Tangl and Mituch: "Pflüger's Archiv," 1908, cxxi, 437; Tangl: *Ibid.*, 423.

[3] Glaser: "Biochemische Zeitschrift," 1912, xliv, 180.

There is no change in the intensity of the oxidation processes in women during menstruation, a fact first shown by L. Zuntz[1] and confirmed by Du Bois.[2]

Schrader[3] showed that there was a retention of protein nitrogen in six women either during the whole menstrual period or during the first part of it. This is in compensation for the loss of blood.

During pregnancy in the higher animals not only must there be growth of the breasts, of the uterine musculature, and of the embryo itself, but there must be energy expended in maintaining the new organism; hence the appetite of the mother increases during pregnancy. Magnus-Levy[4] finds an increased requirement for oxygen on the part of the mother as pregnancy progresses. His table is as follows:

	Oxygen in C.C. per Min.
Non-pregnant	302
Third month of pregnancy	320
Fourth " "	325
Fifth " "	340
Sixth " "	349
Seventh " "	348
Eighth " "	363
Ninth " "	383

Rubner[5] called attention to the fact that the mammalian embryo has no appreciable weight in relation to the mother until the middle of the gestation period, and, in fact, up to this time the metabolism of the mother is usually found to be unchanged.[6] At term, however, the weight of the child is between 5 and 6 per cent. that of the mother, and when the various adnexa are considered the mother loses during par-

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[1] Zuntz, L.: "Archiv für Physiologie," 1906, p. 393.

[2] Gephart and Du Bois: "Archives of Internal Medicine," 1916, xvii, 907.

[3] Schrader: "Zeitschrift für klinische Medizin," 1894, xxv, 72.

[4] Magnus-Levy: "Zeitschrift für Geburtshülfe u. Gynäkologie," 1904, lii, 116. Also see Magnus-Levy: von Noorden's "Handbuch des Stoffwechsels," 1906, i, 409.

[5] Rubner: "Archiv für Hygiene," 1908, lxvi, 177.

[6] Zuntz: "Ergebnisse der Physiologie," 1908, vii, 430; "Archiv für Gynäkologie," 1910, xc, 452.

turition the equivalent of 20 per cent. of her postpartum weight.

Experiments which were carried out by Carpenter and Murlin[1] present an admirable picture of metabolism under the change in conditions effected by parturition. These authors investigated the heat production of three pregnant women in the "bed calorimeter" of the Carnegie Nutrition Laboratory and followed this with similar determinations upon the same women after parturition, each woman being placed in the calorimeter several times, alone and also with her offspring. Observations were made during one to three weeks preceding parturition and during about two weeks following the event.

A summary of the results is presented in the following table:

METABOLISM BEFORE AND AFTER PARTURITION. THE METABOLISM OF THE CHILD WAS DETERMINED BY DIFFERENCE

	Weight in Kg.	Calories per Hour.	Calories per Sq. M. (Meeh).	Calories per Kg. per Hour.
Case I:				
Before parturition	63.0	60.7	31.4	0.96
After parturition	51.4	53.9	31.7	1.05
Difference	11.6	6.8		
Child	2.7	7.3	30.5	2.70
Case II:				
Before parturition	58.0	64.7	35.1	1.11
After parturition	48.5	59.0	36.2	1.21
Difference	9.5	5.7		
Child	3.4	9.8*	34.9	2.88
Case III:				
Before parturition	69.1	70.6	34.0	1.02
After parturition	60.1	60.4	31.9	1.00
Difference	9.0	10.2		
Child	3.2	9.3	34.8	2.90
Average:				
Before parturition	63.4	65.3	33.4	1.03
After parturition	53.3	57.8	33.2	1.09

* Child cried during the experiments.

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[1] Carpenter and Murlin: "Archives of Internal Medicine," 1911, vii, 184.

In cases I and III the metabolism of the child alone was almost exactly equal to the decrease of the metabolism of the woman which ensued after parturition. The authors point out that during parturition the mother loses a considerable weight of material, such as liquor amnii, blood, membranes, placenta, etc., which themselves participate little or not at all in the production of heat. In the cases here cited the heat production of the newborn infant averages 2.6 times that of the mother when the calculation is based upon the calories produced per kilogram of body weight. It is probable, though not experimentally demonstrated, that the youthful, growing protoplasm *in utero* is also endowed with a high metabolism per kilogram of body weight. In the pregnant condition the average weight of these three women was 63 kilograms, and 33.4 calories were produced per square meter of surface. After parturition the average weight was 53 kilograms and the heat production 33.2 calories per square meter of surface. Using Meeh's formula, the average heat production of women between twenty and fifty years old, as determined by Benedict and Emmes,[1] is 32.3 calories per square meter of surface. Herein lies a most remarkable confirmation of the "law of skin area" (see p. 129). Notwithstanding a sudden loss of 10 kilograms, or nearly 20 per cent. of the body weight, as well as the loss of tissues with very uneven capacities of heat production, the sum total of energy production is not altered by gestation or parturition from the common standard of mammalian metabolism as based upon the surface area.

The three mothers nursed their children throughout the days of experimentation. It appears that lactation does not increase the heat production. This is not strange, since the rearrangement of food materials in the preparation of milk depends upon hydrolytic cleavages and syntheses which involve hardly any thermal reactions, and also because it is

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[1] Benedict, F. G., and Emmes, L. E.: "Journal of Biological Chemistry," 1915, xx, 253.

known also that the secretory activity of a gland, such as the kidney when it eliminates urea or sodium chlorid in increased quantity, has no influence upon the total heat production of the body.

The findings of Hasselbalch[1] are not essentially different from those of Carpenter and Murlin.

The composition of the urine, as regards its various constituents, is scarcely changed in pregnancy. Thus, Murlin and Bailey[2] found that the output of ammonia was not increased, that the relative quantity of urea decreased because of protein retention, and that the quantity of oxidized inorganic sulphur also decreased for the same reason, retention for protein synthesis. The "creatinin coefficient" fell, which the authors explain as being due to the addition of inert material to the mother's body.

On empirical grounds von Winckel[3] for many years used the following diet for pregnant women with, he says, "excellent results":

Protein	90 grams.	369 calories.
Fat	27 "	251 "
Carbohydrates	200 "	820 "
Total		1440 calories.

This certainly seems a very low ration and one hardly compatible with furnishing the full calorific requirement. It was employed to prevent an excessive growth of the child within the uterus.

Murlin[4] has made experiments on the total metabolism in pregnant dogs. From one animal a single puppy was born as the result of a first pregnancy and a litter of five from a later one. The following results were obtained:

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[1] Hasselbalch: "Skan. Archiv für Physiologie," 1912, xxvii, 1.

[2] Murlin and Bailey: "Archives of Internal Medicine," 1913, xii, 288.

[3] von Winckel: von Leyden's "Handbuch der Ernährungstherapie," 1904, ii, 469.

[4] Murlin: Proceedings of the American Physiological Society, "American Journal of Physiology," 1909, xxiii, p. xxxii.

Day from Parturition.	Date.	Excreta.		Calories of Metabolism.	
		Total N.	Total C.		
Third before	June 23	8.6	59.4	551.3	One puppy born. Weight, 280 grams.
First after	June 27	8.4	65.8	640.6	
Nineteenth after	July 15	5.3	51.6	505.3	Sexual rest.
Third before	Dec. 11	6.8	74.7	764.9	Five puppies born. Weight, 1560 gms.
First after	Dec. 15	8.3	100.6	1058.8	

The increase of metabolism which can be attributed to the pregnant condition may be found by subtracting the metabolism during sexual rest from that observed just before parturition. By so doing the following figures were obtained:

First pregnancy, 551.3 — 505.3 = 46 calories daily for one puppy of 280 grams.
Second pregnancy, 764.9 — 505.3 = 259.6 calories daily for five puppies of 1560 grams.

This extra metabolism was proportional to the weight of the puppies at birth. In the case of the first pregnancy the extra metabolism was 164, and in the second 165 calories per kilogram of puppy dog delivered three days later.

It is interesting to note that the mother and her five newly born puppies together produced twice as much heat as did the non-pregnant mother alone. The experiments were all made at a temperature of between 27° and 28° C. It is evident that the puppies suckled by the mother and exposed to the outside temperature had a larger metabolism than they had had *in utero*. For the proper maintenance of the five offspring the mother with a normal metabolism of 505 calories would have to produce milk to provide for a metabolism of about 550 calories in the puppies, and still more to furnish material for their rapid growth.

Ostertag and Zuntz[1] report that a sow may yield a milk rich in fat (12.9 per cent.), and in such quantity that the energy

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[1] Ostertag and Zuntz: "Landwirtsch. Jahrbücher," 1908, xxxvii, 226.

content may amount to from two- to fivefold that required for the mother sow's metabolism.

An extraordinary phenomenon which has been observed in dogs and rabbits is that during the early weeks of pregnancy there is a loss of nitrogen from the mother's body even when the food ingested would be entirely sufficient to maintain nitrogen equilibrium under usual circumstances.[1] Jägerroos quotes Ver Ecke's description of this as "the sacrifice of the individual for the good of the species." It seems certain that the development of the fetus is accompanied by the destruction of the maternal protoplasm, perhaps, as Murlin has suggested, in order to afford hereditary building stones for the laying down of the youthful protoplasm in accordance with the type characteristic of the species.

This is the period of the "morning sickness," established in pregnant women during the fourth to sixth week, and accompanied by lack of appetite, vomiting, emaciation, and usually sallowness of face. Dissimilation of tissue and gastrointestinal disturbances are accompanying phenomena.

One of Murlin's[2] experiments covering the period of gestation in a dog is given below:

WEEKLY NITROGEN BALANCE IN A PREGNANT DOG

Week.	Calories in Food per Day.	N in Diet.	N in Excreta.	N to Body.
I	900	52.287	63.116	−8.83
II	976†	56.063	60.893	−4.83
III	976	56.063	62.031	−5.97
IV	976	56.063	64.508	−8.44
V	976	56.063	62.594	−6.53
VI	976	56.063	60.064	−4.00
VII	976	56.063	54.262	+1.80
VIII	976	56.063	47.042	+9.02
IX*	976‡	32.036	25.867	+6.25

* Four days only. † 69.7 calories per kilogram. ‡ 61.0 calories per kilogram.

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[1] Hagemann: "Inaugural Dissertation" Erlangen, 1891; Jägerroos: "Archiv für Gynäkologie," 1902. lxvii, 517.

[2] Murlin: "American Journal of Physiology," 1910, xxvii, 177.

This shows the large loss of maternal protein commencing immediately after conception and continuing for six weeks. Only during the last two weeks is there a marked conservation of protein as manifested in the pronounced nitrogen retention.

Some very instructive experiments have been performed to ascertain the course of the protein metabolism before and after pregnancy in women.

Zacharjewski[1] investigated the nitrogen metabolism of 9 pregnant women. In 3 primiparæ, nourished on diets containing an average of 16.5 grams of nitrogen, there was an average daily retention of 1.4 grams in the mother's organism for thirteen days before parturition. In 6 multiparæ the diet contained 20.6 grams of nitrogen, and there was a daily retention of 5.12 grams of nitrogen during the last eighteen days of pregnancy. The figures correspond to a considerable construction of protein tissue within the organism. After childbirth there was always a loss of tissue nitrogen by the mother. In 1 case nitrogen equilibrium was established on the fifth day, and in another on the fourth. In 6 cases the loss of body nitrogen continued over a longer time. Zacharjewski says that the process of involution of the uterus is greatest during the first five to seven days after delivery, and the high nitrogen output from the mother is the result of this. After the elimination which is due to these regressive changes there is a retention of nitrogen. This is probably attributable to the building up of the mammary glands, for Slemons[2] shows that nitrogen equilibrium, once established, was constantly maintained in a woman who did not nurse her child.

The complete record of the nitrogen elimination of a nursing mother, one of Slemons' cases, is here reproduced. It is especially instructive on account of the constancy of the quantity of nitrogen in the diet. The woman was a negress who gave birth to a healthy, vigorous child.

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[1] Zacharjewski: "Zeitschrift für Biologie," 1894, xxx, 405.

[2] Slemons: "Johns Hopkins Hospital Reports," 1904, xii, 121.

PROTEIN METABOLISM BEFORE AND AFTER CHILDBIRTH

(Weights are in Grams)

Days Before and After Delivery.	N in Food.	N in Urine.	N in Feces.	N in Milk.	N in Lochia.	N Balance.
11	20.5	11.9	0.53	..	..	+8.12
10	19.2	16.6		..	..	+2.07
9	18.0	10.9		..	..	+6.57
8	16.9	17.1		..	..	−0.77
7	11.3	13.7		..	..	−2.95
6	19.2	13.3		..	..	+5.39
5	19.2	12.1		..	..	+6.57
4	19.2	14.1		..	..	+4.54
3	18.0	12.3		..	..	+5.12
2	14.9	12.3		..	..	+2.06
1	8.0	11.5		..	..	−4.00
Delivery	4.2	8.4		..	3.15	
1	7.1	13.3	1.14	..	2.31	−9.66
2	13.7	13.2		0.15	1.99	−2.79
3	19.0	15.8		1.04	1.61	−0.57
4	19.0	18.8		1.99	1.19	−4.13
5	20.0	15.6		2.02	1.05	+0.15
6	20.0	21.8		2.15	1.4	−6.5
7	19.0	18.1		2.02	0.84	−3.14
8	11.0	16.8		2.02	0.28	−9.2
19	19.8	12.1	1.6	1.18	..	+4.89
20	18.8	15.3		1.29	..	+0.57
21	19.9	13.3		1.57	..	+3.39
22	17.3	9.7		1.58	..	+4.39
23	18.0	13.9		1.85	..	+0.68
24	18.75	11.4		2.03	..	+3.72
25	19.0	15.6		1.58	..	−0.16

During the last days of pregnancy there was an average daily storage of 2.98 grams of nitrogen, and for eight days of the puerperium an average loss of 4.5 grams. Later, between the nineteenth and twenty-fifth days after parturition, there was an average daily storage of 2.52 grams of nitrogen. This may have been for the purpose of increasing the size of the breasts. It must be remembered that even during the period of involution an increase in the mammary glands may have been taking place at the expense of protein derived from the uterus. So the debit balance of nitrogen during this period may not represent all the protein change taking place.

An elaborate experiment upon the subject of the metabolism of the pregnant woman was carried out by Hoffström,[1] and extended over the period of the last twenty-three weeks of pregnancy. He computes the probable composition of the ovum at the end of the sixteenth week and compares that with the estimated composition of the child at birth, and also computes the constituents of the food retained for the growth of the child and the mother:

	Retained from Food During Twenty-three Weeks.			Composition of Ovum, Sixteenth Week.
	Total.	For Mother.	For Fetus.	
	Grams.	Grams.	Grams.	Grams.
N.	310.05	208.57	101.48	4.28
P.	55.88	34.0	18.0	0.67
Ca.	34.31	4.2	30.12	0.38
Mg.	2.44	1.46	0.98	0.026

There was an irregular retention of magnesium. Rapid growth of the fetus began during the twenty-ninth week of pregnancy, at which time the calcium retention by the organism greatly increased and the excretion of calcium in the feces of the mother diminished. The retention of materials by the mother herself represents the requirement for the growth of the uterus, the breasts, the gluteal and leg muscles.

Hoffström gives the following computation of the growth of the fetus:

GROWTH OF THE HUMAN FETUS COMPUTED FROM THE TABLES OF MICHEL

Week of Pregnancy.	N.		P.		Ca.		Mg.	
	Content of Ovum.	Added per Week.	Content of Ovum.	Added per Week.	Content of Ovum.	Added per Week.	Content of Ovum.	Added per Week.
16	4.28	1.13	0.67	0.20	0.38	0.41	0.026	0.017
20	8.81	..	1.47	..	2.03	..	0.095	..
21	..	1.81	..	0.25	..	0.43	..	0.017
28	23.28	..	3.58	..	5.39	..	0.234	..
29	..	6.87	..	1.28	..	2.09	..	0.064
40	105.76	6.87	18.93	1.28	30.51	2.09	1.004	0.064

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[1] Hoffström: "Skan. Archiv für Physiologie," 1910, xxiii, 326.

It is obvious that during the last ten weeks of pregnancy a diet which is rich in calcium is indicated, or there may be a withdrawal of calcium from the mother's bones. Cows' milk contains much calcium and is a highly desirable addition to the dietary of the pregnant woman. (See p. 374.)

Rubner and Langstein[1] have investigated the metabolism of two prematurely born infants. One of them was born at the end of the seventh month of pregnancy and weighed 2050 grams. On the eighth day the child weighed 1900 grams, and then gained an average of 28 grams daily until the twenty-seventh day, when it weighed 2360 grams. At this point respiration experiments were introduced. During the next eleven days the child gained 39 grams daily. During this same period the child received each day 1.04 grams of nitrogen in milk and retained 0.52 gram, or 50 per cent. of the intake. At this period, which would have corresponded to the beginning of the eighth month of pregnancy, the addition of protein to the child amounted to only one-half that computed by Hoffström for the fetus of the same age. The fat retained per day averaged 14.6 grams. The diet contained 126 calories per kilogram of body weight, of which 73 were used for heat production (973 calories per square meter per day) and 53 were deposited in the growing infant. In all, 42 per cent. of the calories ingested in the food were retained for growth, a remarkably large amount. The so-called "growth impulse" must have been very great. The second prematurely born infant showed the same capacity for protein retention as the first, but the amount of fat retained was much less.

The mother, previously described as having been investigated by Slemons, had plenty of milk, and the baby gained an average of 30 grams a day during the first forty days of his life.

Slemons remarks that the low protein metabolism, as indicated by the urinary nitrogen of the period of settled lactation,

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[1] Rubner and Langstein: "Archiv für Physiologie," 1915, p. 39.

is a proof that there can be no important production of milk fat from protein.

In the above experiment it will be noticed that the nitrogen of the milk is small in quantity as compared with the urinary nitrogen. On a strictly vegetarian diet the relation would change. Thus Voit[1] found 48.8 grams of nitrogen in the milk of a cow and 93.7 grams of nitrogen in her urine for the same period.

The influence of nutrition on the production of milk has been the object of countless investigations, but unfortunately most of these experiments have been conducted for commercial purposes on cows and goats. These animals, with their fundamental ration consisting of hay, do not allow of the ingestion of simple foods. On the other hand, the milk supply of even a large bitch is very limited in quantity and is with difficulty obtained. The writer is not aware of any systematic observations on the composition of human milk as influenced by food, although such researches would seem of great importance.

Perhaps the most valuable research which can today be used is an old one of Voit[2] upon a bitch weighing 34 kilograms. It confirmed the previous work of Kemmerich and of Ssubotin, and has since been verified by Grimmer.[3] The animal was given meat alone, meat and starch, meat and fat, starch alone, fat alone, and was also starved. The influence upon the milk secretion was found to be comparatively small. The research is a model of completeness, the plan of which could well be copied in an experiment on a human being.

A part of the results are given on page 392.

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[1] Voit: "Zeitschrift für Biologie," 1869, v, 122.

[2] Voit: *Ibid.*, 137.

[3] Grimmer: "Biochemische Zeitschrift," 1914, lxviii, 311.

INFLUENCE OF DIET ON THE COMPOSITION OF THE MILK OF A DOG WEIGHING 34 KILOGRAMS

Food.				Milk.						
Day.	Meat, Grams.	Other Food, Grams.	N, Grams.	Amount C.C.	N, Grams.	Fat, Grams.	Sugar, Grams.	Protein, Per Cent.	Fat, Per Cent.	Sugar, Per Cent.
6....	1000	300 starch	34	115	1.1	8.8	3.1	5.97	7.70	2.71
7....	1000	200 fat	34	144	1.4	10.8	3.8	6.86	7.50	2.67
8....	1000	200 fat	34	135	1.1	11.3	2.9	6.22	8.39	2.15
9....	Mixed diet	....	..	151	1.4	13.9	3.4	6.37	9.22	2.24
10....	500	400 starch	17	138	1.2	11.3	3.8	5.83	8.19	2.78
11....	500	300 fat	17	168	1.6	16.5	4.2	6.06	9.83	2.52
12....	Starv.	....	..	149	1.5	13.8	3.9	6.36	9.24	2.65
13....	Starv.	....	..	118	1.0	12.2	3.0	5.62	10.32	2.58
14....	..	500 starch	..	137	1.1	10.1	4.3	5.41	7.39	3.11
16....	2000	....	68	158	1.6	16.1	4.4	6.68	10.17	2.82
17....	2000	....	68	161	1.7	14.7	4.7	6.78	9.11	2.91

The largest quantity of milk, as well as the richest in protein, was obtained when meat or meat and fat were ingested. Curiously enough, a diet of 500 grams of meat and 300 grams of fat gave milk of the same amount and quality as did 2000 grams of meat. It is usually said that a large protein diet stimulates the milk secretion; but this may also be due indirectly to the development of the gland cells.

The milk-sugar content was scarcely affected by the diet, although a slight percentage increase was observed after starch ingestion.

The fat content was increased in starvation to its highest percentage. It was not very greatly affected by adding fat to a meat diet and it was greatly reduced by giving carbohydrates.

The action of fasting on the fat content of milk is better shown in the herbivorous goat. The writer[1] gave a milch goat a constant diet of hay, cornmeal, and bran, starved the animal for two days, and then continued the former diet. The fat content of the milk was determined. The results were as follows:

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[1] Lusk: "Zeitschrift für Biologie," 1901, xlii, 42.

Milk in C.C.	Fat in G.	Fat in Per Cent.	
460	26.50	5.76	
470	25.90	5.52	
383	23.90	6.23	Starvation.
198	18.35	9.27	
232	18.75	8.08	
298	16.30	5.47	
348	14.04	5.61	
362	22.30	6.16	
490	27.70	5.66	

In fasting, therefore, the fat content in the milk of the herbivorous goat approaches that contained in the carnivorous dog. With a return to the normal diet the fat content in goat's milk is reduced to its former level.

Morgen, Beger, and Fingerling[1] find that a diet rich in carbohydrate and poor in fat produces in sheep and goats a poor milk containing little fat, although the general condition of the animals remains perfect. Addition of protein increases the quantity of the milk without changing the low fat percentage. Replacement of some of the carbohydrate with isodynamic quantities of fat, up to 0.5 to 1.0 gram per kilogram of animal, largely increases the fat content of the milk and thereby its nutritive value.

Contrary to this is Jordan's[2] statement that the amount of fat in the fodder is without influence upon the fat content of a cow's milk. Here the breed of the cow and not the diet is the determining factor. The German agricultural stations have recently reached the same conclusion. Morgen[3] states that the principal cause of the difference in the results of the experiments on cows and on sheep and goats lies in the fact that the smaller animals produce more milk for their weight than do cows, and, therefore, the milk production is much more dependent on the food supply.

Newer work by Prausnitz[4] concludes that although food

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[1] Morgen, Beger, and Fingerling: "Landwirtschaft. Versuchsstationen," 1904, lxi, 1.

[2] Jordan and Jenter: "New York Agricultural Experiment Station," 1897, Bulletin 132; 1901, Bulletin 197.

[3] Morgen, Beger, Fingerling, and Westhauser: "Landwirtschaft. Versuchsstationen," 1908, lxix, 295.

[4] Helle, Müller, Prausnitz, and Poda: "Zeitschrift für Biologie," 1912, lviii, 355.

does not determine the quantity of protein, lactose, or ash in cows' milk, yet the percentage of fat, and hence the caloric value of the liter of milk, may be considerably influenced by variations in the diet.

It has long been known that ingested fat may appear in the milk of an animal. Gogitidse[1] has shown that after giving linseed oil to sheep their milk fat may contain 33 per cent. of linseed oil. He also finds[2] that the fat of linseed oil passes readily into human milk, and that the fat of hempseed, while influencing the composition of the milk, greatly depresses lactation during the period of its ingestion.

Hart and Humphrey[3] have shown that the protein content of the milk varies very little even though a cow may be losing her own flesh to furnish the milk. Thus, when a cow was given a food with a "nutritive ratio" of 1 : 8, that is, 1 part of protein to 8 parts of carbohydrate and fat, a positive nitrogen balance was present provided milk protein was given in the diet, but when protein was administered in the biologically lower form of wheat protein, a negative nitrogen balance resulted. The quantity of protein in the milk, however, remained unchanged.

These facts are shown in the following table:

	N Intake per Week, Grams.	Fecal N, Grams.	Absorbed N, Grams.	Urine N, Grams.	Milk N, Grams.	Balance N, Grams.
Wheat ration......	953	404	549	464	227	−142
Milk ration.......	968	350	618	286	220	+112

"Milking the flesh off the back" is, therefore, a reality. During lactation a ration high in protein is wisely dictated and the biologic status of the protein must also be considered.

According to similar laws, Fingerling[4] finds that a fodder deficient in calcium has no effect upon the calcium content

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[1] Gogitidse: "Zeitschrift für Biologie," 1904, xlv, 365.
[2] Gogitidse: *Ibid.*, 1905, xlvi, 403.
[3] Hart and Humphrey: "Journal of Biological Chemistry," 1915, xxi, 239.
[4] Fingerling: "Landwirtschaft. Versuchsstationen," 1911, lxxvi, 1.

of the milk, the organism providing this material. Furthermore, Lauder and Fagan[1] found that the addition of 225 grams of calcium phosphate to a fodder already containing the same content of that salt did not alter the calcium content of cows' milk. Von Wendt[2] states that ingestion with the fodder of sodium chlorid, calcium carbonate, calcium hydrogen phosphate, calcium glycerophosphate, sodium phosphate, or magnesium bromid is without definite influence upon the composition of the milk. The lactic glands, therefore, prepare a fluid of very definite composition specifically designed for the offspring of the species.

How may the various effects of diet be explained? The subject requires a knowledge of the processes going on in the mammary gland, and these are not certainly known. It has been generally believed that the cells of the mammary glands undergo a fatty metamorphosis and, themselves breaking up, pass into the milk (Voit, Heidenhain). The milk under these circumstances might be regarded as the substance of an organ, made fluid.

Schäfer,[3] however, believes the process to be one of secretion similar to that in the salivary glands, where the cells prepare the special constituents and pass them on to the lumen. Thus casein, like ptyalin, may be specially elaborated within gland cells.

If this be the true explanation, the influence of food, in the writer's opinion, may be readily explained. An increased protein ingestion furnishes the digestive products of this substance in liberal quantities and may increase the activity of the gland.

The milk-sugar content of the milk remains remarkably constant. Cremer,[4] for example, has shown that the percentage of milk-sugar in the milk is unchanged in the cow

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[1] Lauder and Fagan: "Proceedings of the Royal Society of Edinburgh," 1914–15, xxxv, 195.

[2] von Wendt: "Skan. Archiv für Physiologie," 1909, xxi, 89.

[3] Schäfer: "Text-book of Physiology," 1898, i, 667.

[4] Cremer: "Zeitschrift für Biologie," 1899, xxxvii, 78.

after diminishing the sugar content of the animal by inducing phlorhizin diabetes.

To explain the fat content of the milk the writer offers the following theory: When for any reason sufficient sugar is not oxidized in the body cells, these sugar-hungry cells attract fat. It has already been seen that the glycogen and fat content of the liver are antagonistic. Before lactation sets in, the cells of the mammary glands oxidize sugar and there is no great attraction for fat. It is believed that milk-sugar cannot be formed in any great quantity before parturition, because it occurs in the urine only *postpartum*.[1] That milk-sugar is not formed outside of the mammary glands was demonstrated by Moore and Parker,[2] who completely removed these glands from a goat during the period of gestation, and later at the time of parturition found no sugar in the urine. Had milk-sugar, which cannot be oxidized by the organism, been formed outside the glands it would have accumulated in the blood and have been eliminated in the urine. When in the process of lactation the glucose furnished by the blood is converted into milk-sugar (which cannot be burned within the organism), the mammary cell becomes a sugar-hungry cell which at once attracts fat from the blood. This theory of the writer explains the production of milk fat by the process of infiltration. The variation of the percentage of fat in the milk may be explained by the quantity of fat in the blood. During starvation the blood becomes rich in fat on account of the transportation of tissue fat to the cells. Administration of sugar at once reduces the supply of fat in the blood. But if fat be ingested with carbohydrates the blood becomes rich with this fat and affords material for a rich milk.

Administration of good cream with a substantial mixed diet is highly to be recommended for nursing mothers. The daily production of a liter of milk, which has a value of 640 calories, indicates the necessity of no small addition to the

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[1] Lemaire: "Zeitschrift für physiologische Chemie," 1896, xxi, 442.

[2] Moore and Parker: "American Journal of Physiology," 1900, iv, 239.

daily ration, if the woman is to bear satisfactorily the strain of lactation. Probably this extra nourishment is best given in the form of fat.

Should the fat of the milk disagree with the infant, the trouble may be due to the kind of fat ingested by the mother. If, however, the indigestion be due to a large percentage of fat, a carbohydrate diet may be used to reduce the percentage in the milk.

It may be added that Völtz and Paechtner[1] report that after moderate ingestion of alcohol only minimal quantities of it are found in human milk.

A very important fact regarding the nutrition of the young is that the milk of one race is specifically adapted to the growth of the offspring of that particular race. Bunge[2] found that dogs' milk had an ash of exactly the same composition as the ash of the newborn puppy. The ash of the milk was, therefore, perfectly adapted for the construction of new puppy tissue. It was, however, very different in composition from human, or cows', or other milk. Only in the case of iron is the quantity lower than corresponds to the composition of the offspring, but this factor is offset by the fact that the animal when newborn is richer in iron than it is at any other period of life. Not only this, but the caseins of different milks are different in chemical behavior. And besides this, the rennin of the stomach is said to be specifically adapted for the coagulation of the casein produced by the female of the same race.[3]

Furthermore, the percentage quantity of the constituents in the milk is dependent upon the rapidity of the growth of the organism. Bunge[4] has shown this in the following comparative table:

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[1] Völtz and Paechtner: "Biochemische Zeitschrift," 1913, lii, 73.

[2] Bunge: "Zeitschrift für Biologie," 1874, x, 326.

[3] Kiesel: "Pflüger's Archiv," 1905, cviii, 343.

[4] Bunge: "Lehrbuch der physiologischen Chemie," 1898, p. 118.

	Time in Days for the New-born Animal to Double Its Weight.	100 Parts of Milk Contain		
		Protein.	Ash.	Calcium Oxid.
Man	180	1.6	0.2	0.328
Horse	60	2.0	0.4	0.124
Calf	47	3.5	0.7	0.160
Kid	19	4.3	0.8	0.210
Pig	18	5.9		
Lamb	10	6.5	0.9	0.272
Dog	8	7.1	1.3	0.453
Cat	7	9.5		

Camerer[1] finds that human milk, drawn three to twelve days after parturition, contains 0.2 milligram of iron (Fe_2O_3) per 100 c.c., while the later milk contains 0.1 milligram. The quantity is decreased if the environment or the condition of the mother be poor.[2] Edelstein and Csonka[3] state that 1 liter of cows' milk contains 0.7 milligram of Fe_2O_3 (0.6 to 1 mg.), which is one-third to one-half the quantity contained in human milk. Using the customary methods of infant feeding with cows' milk, the infant obtains too little iron.

Blauberg[4] reports the following percentage absorption of the ash of cows' and human milk:

Kind of Milk.	Subject.	Per Cent. Milk Ash Absorbed.
Cows'	Infant.	60.70
Diluted cows'	"	53.72
Human	"	79.42
Human	"	81.82
Cows'	Adult.	53.20

The quantity of calcium in cows' milk is in excess of the needs of the human infant.

The absorption of the energy-containing constituents of the milk is remarkably constant. This is illustrated in the following table made from Rubner's experiments,[5] which shows the physiologic utilization of the total calories of milk:

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[1] Camerer: "Zeitschrift für Biologie," 1905, xlvi, 371.

[2] Jolles and Friedjung: "Arch. für experimentelle Path. und Pharm.," 1901, xlvi, 247.

[3] Edelstein and Csonka: "Biochemische Zeitschrift," 1911–12, xxxviii, 14.

[4] Blauberg: "Zeitschrift für Biologie," 1900, xl, 44.

[5] Rubner: *Ibid.*, 1899, xxxviii, 380. For further statistics of absorption consult Tangl: "Pflüger's Archiv," 1904, civ, 453.

	Per Cent. of Calories Absorbed.
Human milk	91.6 to 94.0
Diluted cows' milk	90.7
Diluted cows' milk + milk-sugar	92.2
Same given to stunted infant	87.1
Cows' milk given to an adult	89.8

As regards the relative composition of average cows' and human milk five and one-half months after parturition, the following comparison may be made:

PERCENTAGE COMPOSITION OF COWS' AND HUMAN MILK

	Cows'.		Human.	
	I.[1]	II.[2]	I.[3]	II.[4]
Protein	3.41	3.2	1.0	1.52
Fat	3.65	3.9	3.0	3.28
Milk-sugar	4.81	5.1	6.4	6.50

Or, expressed in the relative calorific value of the different constituents, this comparison may be given:[5]

PERCENTAGE DISTRIBUTION OF CALORIES IN COWS' AND HUMAN MILK

	Cows'.	Human.
	I.	I.
Protein	21.3	7.4
Fat	49.8	43.9
Milk-sugar	28.9	48.7

Here, then, there are tremendous differences of composition, which fact forces the conclusion that cows' milk is not to be substituted for human milk in rearing a child.

Patein and Daval[6] find that human milk after the first month of lactation contains but 0.8 to 1 per cent. of casein.

Another distinction between cows' and human milk is that the former contains but little extractive nitrogen, while the latter may contain 18 to 20 per cent.[7] in that form. These nitrogenous extractives contain a considerable amount of

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[1] Rubner: Von Leyden's "Handbuch," 1903, i, 95.

[2] Van Slyke, "Modern Methods of Testing Milk and Milk Products," 1907. Average of 5552 American analyses.

[3] Rubner and Heubner: "Zeitschrift für ex. Pathologie und Therapie," 1905, i, 1.

[4] Söldner: "Zeitschrift für Biologie," 1896, xxxiii, 66. Average of the milk of 5 women.

[5] Rubner: "Energiegesetze," 1902, p. 418.

[6] Patein and Daval: "Journal de Pharm. et de Chimie," 1905, xxii, 193.

[7] Rubner and Heubner: *Loc. cit.*

carbon. Meigs and Marsh[1] state that human milk contains 1 per cent. of unknown extractive substances which are almost free from nitrogen. This is probably one of the causes of the increase of the $\frac{C}{N}$ ratio (see p. 38) to over unity in the urine of breast-fed infants.

From the standpoint of chemical analysis Abderhalden[2] could find no distinctive quantitative difference between the amounts of various amino-acids in human and bovine milks.

A recent analysis[3] presents the following data as regards the probable composition of human milk:

	Per Cent.
Fat	3.30
Lactose	6.50
Proteins combined with calcium	1.50
Calcium chlorid	0.059
Monopotassium phosphate	0.069
Sodium citrate	0.055
Potassium citrate	0.103
Monomagnesium phosphate	0.027

The large protein content of cows' milk may be bad for the child. In the first place it clots in a heavy mass in the baby's stomach; and in the second place, even though it be digested, it is relatively much above the requirement of the organism, and its specific dynamic action increases the amount of heat produced. (See p. 406.)

If cows' milk be diluted with 2 or more parts of water its protein content may approach that of human milk and its precipitation by rennin in the stomach is in the form of flakes. The writer's father,[4] following a suggestion of Abraham Jacobi, used oatmeal or barley water as a diluent of milk given to babies. The precipitation of cows' casein takes place in very fine flakes when the milk is mixed with barley water, as was shown by Chapin.

Chapin's observations, in which the writer assisted, have been confirmed by White,[5] who says that this action is due to the presence of $\frac{3}{4}$ to 1 per cent. of dissolved starch.

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[1] Meigs and Marsh: "Journal of Biological Chemistry," 1913–14, xvi, 147.

[2] Abderhalden and Langstein: "Zeitschrift für physiologische Chemie," 1910, lxvi, 8.

[3] Bosworth: "Journal of Biological Chemistry," 1915, xx, 707.

[4] Lusk, W. T.: "Science and Art of Midwifery," 1891, p. 258.

[5] White: "Journal of the Boston Society of Medical Sciences," 1900, v, 130.

The dilution of cows' milk, however, reduces the quantity of fat and carbohydrates, and these must therefore be added to the milk in order to make a proper diet for a child.

To obtain a sufficient fat content, "top milk," rich in fat, may be taken from milk which has been standing, and may be mixed with water. Milk-sugar may then be added.

Such a milk, called "modified milk," was first introduced by Rotch, of Boston. Infants are brought up on it with greater success than was the case when undiluted cows' milk was given.

Human milk has a varying calorific value dependent largely on the amount of fat present. Thus Schlossmann[1] finds that the calorific value per liter of nineteen samples of milk from 19 women averages 719 calories, with a maximum of 876 and a minimum of 567. The milks having the largest fuel value contained 5.2 to 5.1 per cent. of fat, while that having the lowest contained only 1.8 per cent.

The amount of the child's metabolism is dependent on his size. Rubner states that a baby weighing 4 kilograms produces 422 calories, an adult weighing 40 kilograms, 2106 calories, but that the metabolism per unit of area is the same.

Rubner and Heubner[2] summarize their results on the metabolism of differently conditioned children as follows:

	Weight in Kg.	Calories per Sq. Meter of Surface.
Infant of stunted growth	3	1090
Infant at the breast	5	1006
Infant on cows' milk	8	1143
Infant at the breast	10	1219

The metabolism in all these cases was essentially the same per unit of area.

In the last case the very noticeable amount of muscle movement and crying while the child was in the respiration apparatus increased the metabolism. Further details regarding this case give a very complete picture of the metabolism of an infant. The child weighed 4.06 kilograms at birth, and

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[1] Schlossmann: "Zeitschrift für physiologische Chemie," 1903, xxxvii, 340.

[2] Rubner and Heubner: "Zeitschrift für ex. Pathologie und Therapie," 1905, i, 1.

about 10 kilograms at the time of the experiment when five and a half months old. He was given his mother's milk.

The first day of the experiment the child was very uncomfortable on account of his new environment. The last day he was given only a small quantity of tea, and was therefore in a state of practical starvation. The carbon dioxid excretion on these days was as follows:

	Grams of CO_2 in 24 Hours.
First	278.8
Second	219.9
Third	228.1
Fourth	231.1
Fifth	218.2

The diet on the second, third, and fourth days consisted of 1258 grams of human milk per day containing:

Total nitrogen	1.99	grams.
Fat	37.73	"
Milk-sugar	85.5	"

Of the total nitrogen only 1.63 grams were contained in true protein, the rest being in nitrogenous extractives. The percentage composition of this milk is given on page 399. Its actual nutritive value was 634.5 calories.

The balance sheet of the respiration experiment showed the following daily result:

METABOLISM OF AN INFANT

Day.	Food.	N in Food.	N in Urine.	N in Total Excreta.	N Balance.	C in Food.	C in Excreta.	C Balance.
		Grams.	Grams.	Grams.	Grams.	Grams.	Grams.	Grams.
2, 3, 4	Milk.	1.99	1.13	1.53	+0.46	63.7	65.8	−2.1
5	None	....	1.18	1.18	−1.18	....	60.8	−60.8

The infant was nearly in calorific equilibrium during the period of milk ingestion. There were 634.5 available calories in the milk and 660.5 calories produced in the metabolism.

The quantity of the protein metabolism was extremely small, being 9.6 grams according to the usual method of computation. The milk contained protein to the extent of 7 per cent. of its total calorific content. Of this only 5 per cent. was metabolized and 2 per cent. was added to the body. The metabolism of an infant may therefore be maintained on a diet in which 5 per cent. of the energy is supplied by protein and 95 per cent. by fats and carbohydrates.

The specific dynamic action of the milk was almost negligible, the metabolism being approximately the same during the period of feeding as during that of starvation. Curiously enough, the protein metabolism was the same on days of milk ingestion as in starvation. The "wear and tear" quota was covered by a "repair" quota of equal amount. (See p. 282.)

This child gained normally in weight before and after the respiration experiment, but during that time struggling and crying prevented fat addition to the otherwise well-developed normal infant.[1]

Schlossmann and Murschhauser[2] note that, whereas during the first and second days of fasting an infant may eliminate 16 and 15 milligrams of urinary nitrogen per kilogram of body weight, return to a normal diet results in the elimination of only 8 milligrams per kilogram. This illustrates the avidity with which, under favorable conditions, all available protein is used for growth.

W. Camerer, Jr.,[3] showed that a breast-fed infant nine months old may ingest 480 calories in the milk, produce 420 calories in metabolism, and add 60 calories to his body, or 15 per cent. of the energy content of the diet. In this case 40 per cent. of the protein intake was added to the growing organism.

Rubner and Heubner[4] have reported a respiration experiment on a child seven and a half months old nourished with modified cows' milk. The intake was 682.8 calories, the metabolism 593.2, leaving 89.6 calories, or 12.2 per cent. for addition to the child's organism.

It is remarkable that a child's intuitive appetite should

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[1] Heubner: "Jahrbuch für Kinderheilkunde," 1905, lxi, 430.

[2] Schlossmann and Murschhauser: "Biochemische Zeitschrift," 1913, lvi, 355.

[3] W. Camerer, Jr.: "Zeitschrift für Biologie," 1902, xliii, 1.

[4] Rubner and Heubner: *Ibid.*, 1899, xxxviii, 345.

determine the ingestion of nutriment necessary to cover the energy requirement of his organism, and a small addition for normal development. A reduction of 15 per cent. in the intake of food would bring his prosperous growth to a standstill.

Heubner[1] says that the average normal infant requires 100 calories per diem per kilogram of body weight for normal nutrition during the first three months of his life, 90 calories during the second three months, and 80 and less thereafter. The energy content of the food should never sink below 70 calories per kilogram, which is about the maintenance minimum.

The so-called "scientific feeding" of infants is unworthy of the name unless the calorific requirement is carefully considered. From lack of this knowledge babies are frequently systematically starved.

It is evident from this discussion that the fundamental, basal metabolism of the infant cannot be determined during long periods in which crying is an ever-entering factor. Schlossmann and Murschhauser,[2] for example, have found that the metabolism of an infant may double during an hour of movement when the baby would not be quieted, but cried intensely. The resting metabolism of this child five months old was estimated at 859 calories per square meter of surface in twenty-four hours. The same authors[3] have shown that a change of environmental temperature between 22° and 17° C. has no influence upon the heat production of the infant. Hasselbalch[4] in 1904 investigated the metabolism of newborn babies and established the fact that the respiratory quotient of the child at birth was about unity, which indicates that the earliest source of its energy requirement is derived from stored glycogen. This was confirmed by Bailey and Murlin, who also showed that on account of insufficient nourishment the

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[1] Heubner: "Berliner klinische Wochenschrift," 1901, xxxviii, 449.

[2] Schlossmann and Murschhauser: "Biochemische Zeitschrift," 1910, xxvi, 14.

[3] Schlossmann and Murschhauser: *Ibid.*, 1911, xxxvii, 1.

[4] Published in Danish; English translation by F. G. Benedict and Talbot in "The Physiology of the Newborn Infant," 1915, Carnegie Institution Bulletin 233.

respiratory quotient fell to the fasting level within twenty-four hours.

The principal recent work upon this subject of the metabolism of children has been accomplished in the United States. It was begun by John Howland and continued by Benedict and Talbot, and by Murlin and Bailey, and Murlin and Hoobler.

Howland's[1] experiments are the only reported calorimetric observations upon infants, and the close concordance between direct and indirect calorimetry as observed in hourly periods in these experiments gave confidence to subsequent observers that by the careful determination of the respiratory metabolism alone the actual heat production could be readily computed.

Howland gives the following summary of work with a normal male infant (Child I) five months old and with a boy (Child III) six months old who weighed only 3 kilograms and was literally "skin and bones." The children were fed with diluted milk with the addition of milk-sugar:

CORRESPONDENCE BETWEEN DIRECT AND INDIRECT CALORIMETRY IN INFANTS

	Food.	Calories per Sq. M. per Day.		Difference in Per Cent.
		Direct.	Indirect.	
Child I	Milk	1046	1084	2
		1113	1174	
		1196	1164	
	Same + nutrose	1218	1179	3
	Same + nutrose	1204	1180	0.6
		1235	1212	
		1181	1250	
	Fasting	1106	1177	2
		1226	1156	
		1301	1243	
Child III	Milk	858	793	2
		913	933	
	Milk	825	840	

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[1] Howland: "Zeitschrift für physiologische Chemie," 1911, lxxiv, 1; Transactions XV International Congress of Hygiene, 1912, ii, Part 2, 438.

To compute the surface area of children Lissauer's formula ($10.3 \sqrt[3]{\text{Weight}^2}$) is usually employed, though Howland has suggested one of still greater accuracy.

Just as in the case of the adult (see p. 476), the emaciated organism of an infant produces less heat per square meter of surface than the normal organism. Howland reported another case in which he determined the heat production of an eight-year old child, emaciated to a most extreme degree and almost devoid of musculature. The average heat production was 13.2 calories per hour, or 809 per square meter of surface per day.

Lusk[1] pointed out that, whereas the metabolism of the dog and of a human dwarf was about 775 calories per square meter per day under conditions of complete rest, that of the two normal infants who were the subjects of Howland's experiments was 1100 calories per unit of surface. Howland's work furthermore showed that when nutrose was added to the diet there was a pronounced specific dynamic action, the heat production rising from 14.9 to 18.8 calories per hour, an increase of 26 per cent. Vigorous crying also increased the metabolism in the same child from 14.85 to 20.6 calories per hour, an increase of 39 per cent. (See p. 407.)

In 1914 Benedict and Talbot[2] published a monograph which included metabolism studies upon 37 infants, as the result of which they concluded, "We find ourselves thoroughly convinced that the metabolism is determined not by the body surface, but by the active mass of protoplasmic tissue."

Bailey and Murlin[3] published observations upon the metabolism of 6 newborn infants shortly after the publication of a preliminary communication by Benedict and Talbot[4] upon the same subject, which they later reported in detail.[5]

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[1] Lusk: "Transactions XV International Congress of Hygiene," 1912, ii, Part 2, 400.

[2] Benedict and Talbot: "The Gaseous Metabolism of Infants," Carnegie Institution of Washington, 1914, Bulletin 201.

[3] Bailey and Murlin: "American Journal of Obstetrics," 1915, lxxi, 526.

[4] Benedict and Talbot: "Amer. Jour. of Diseases of Children," 1914, viii. 1.

[5] Benedict and Talbot: "The Physiology of the Newborn Infant," Carnegie Institution of Washington, 1915, Bulletin 233.

In the same year Murlin and Hoobler[1] published their results concerning the energy metabolism of 10 hospital children and at the same time summarized the work of their predecessors and contemporaries. They pointed out that the heat production of sleeping children between the ages of two months and one year was about 2.5 calories per kilogram per hour; in other words, they state that 60 calories per kilogram per day may be called the heat production of normal, recently fed, sleeping infants. The newborn babies had a metabolism less than this, which did not exceed 48 calories per kilogram per day. Murlin was the first to emphasize that when age was taken into consideration there was a constancy in the heat production per square meter of surface. Two charts taken from Murlin illustrating the relations described are reproduced on pages 408 and 409, and the chart of Du Bois showing the influence of age on metabolism should also be consulted. (See p. 127.)

In gratifying accord with this interpretation is the more recent announcement of Benedict and Talbot that in 48 newborn infants 80 per cent. of their cases showed a metabolism which was within 6 per cent. of 640 calories per square meter per day. Per kilogram of body weight 48 calories is given by them as the maintenance minimum.

In practical dietetics one must add to the maintenance requirement sufficient nourishment to provide for the crying of the child, and also the very considerable quota to meet the demands of growth.

The amount of energy expended by the crying of an infant will vary with the infant, for during this form of exercise the heat production is raised at least 40 per cent. It is certain that Heubner's figure of 100 calories per kilogram of body weight during the first month of the infant's nutrition is in excess of the requirement. Probably 80 calories per kilogram of body weight will be found to suffice during the whole of the

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[1] Murlin and Hoobler: "Amer. Jour. of Diseases of Children," 1915, ix, 81.

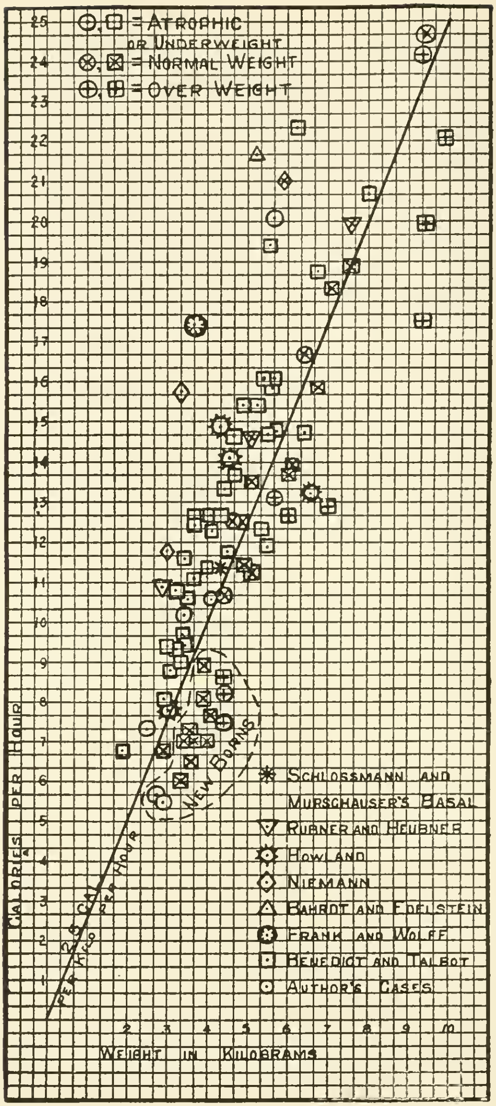

Fig. 24.—Showing relation of heat production to body weight. All infants whose metabolism has been studied by von Pettenkofer or Regnault-Reiset methods.

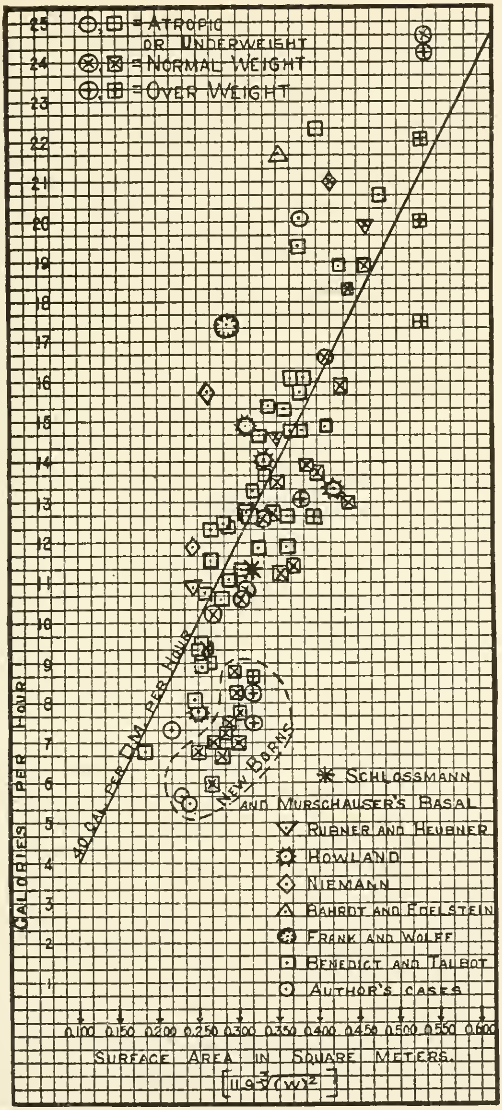

Fig. 25.—Showing relation of heat production to skin surface. All infants whose metabolism has been studied by von Pettenkofer or Regnault-Reiset methods.

first year of life, and the physician should remember very definitely the lower limits. It is not infrequent that a crying infant is merely hungry.

Oppenheimer[1] first called attention to the fact that the growth in grams of normal breast-fed children of the same age may be nearly proportional to the quantity of milk ingested. Here the milk presumably had the same calorific value throughout the experiment, although this could not be determined. The quantity of milk taken at each meal was found by weighing the infant before and after nursing. Oppenheimer's table is here reproduced:

GROWTH IN GRAMS FOR 1 KG. MILK

Month.	Feer's Subject.	Oppenheimer's Subject.
I	33.8	95.0
II	191.2	201.1
III	120.3	138.5
IV	102.6	103.3
V	57.7	120.8

The proportion of growth to milk given was practically the same during the second, third, and fourth months of these children's lives.

That the growth of suckling pigs may be proportional to the calorific value of the milk has been shown by work accomplished by Dr. L. C. Sanford and Dr. Margaret B. Wilson[2] in the writer's laboratory. Newborn pigs of two litters were reared on skimmed cows' milk and on the same milk fortified with 2 and 3 per cent. of glucose or of milk-sugar. The experiments were continued from fourteen to sixteen days. The results obtained in these experiments are thus tabulated:

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[1] Oppenheimer: "Zeitschrift für Biologie," 1901, xlii, 147.

[2] Wilson: "American Journal of Physiology," 1902, viii, 197.

GROWTH OF SUCKLING PIGS

	Wilson.			Sanford and Lusk.		
	Skimmed Milk.	Lactose.	Glucose.	Skimmed Milk.	Lactose.	Glucose.
Weight in grams when born	1,322	1,295	1485	1000	1050	1152
Weight in grams when killed	2,205	2,435	2471	1246	1890	2000
Growth in grams	883	1,140	986	264	838	848
Growth in per cent	66.8	88.0	66.4	26.4	79.7	73.6
Milk fed in c.c.	10,925	11,005	9707	6826	8836	9481
Available calories fed	4,053	5,216	4620	2339	3736	3972
Growth in grams per liter of milk	81	114	101	38	95	89
Growth in grams per 1000 calories fed	218	215	213	114	222	213

It is seen that the growth of the pigs in grams was directly proportional to the calorific value of the food to the organism. The one exception was that of an ill-nourished pig fed with skimmed milk. This was an improperly nourished animal taking too little food and remaining behind his fellows in normal development. But that 5 out of 6 pigs of different litters, of different sizes and differently fed, should have gained in weight respectively 213, 214, 215, 218, and 222 grams per thousand calories in the food ingested seems more than a coincidence.

It may be further calculated that to form 1 kilogram of body substance containing 28.7 grams of nitrogen and 866 calories requires the ingestion of 4637 calories in the food.

A pig doubles in weight in eighteen days after birth. The pig of Dr. Wilson, brought up on skimmed milk with 3 per cent. of milk-sugar added, nearly doubled in weight in sixteen days.

Comparing the fuel value of sows' milk and that of the skimmed cows' milk to which milk-sugar had been added, the following results are significant. Of 100 calories in the food there are:

	Sows' Milk.[1]	Skimmed Milk + 3 Per Cent. Milk-sugar.
Protein	19.5	36.5
Fats	72.0	2.5
Carbohydrates	8.5	61.0

It is apparent from this that normal growth of the young organism may be attained by the replacement of fat by milk-sugar in isodynamic quantity. This fact may become of importance in infant feeding.

Dr. Wilson found, when the pigs reared on these diets were killed and their composition compared with that of 3 pigs of the same litter which were killed at birth, that there was a retention for growth of 18 to 19 per cent. of the energy in the food.

In children Camerer found 15 per cent., Rubner and Heubner 12.2 per cent. so retained.

The percentage of calcium (CaO) in the dry solids of the pigs reared on the various skimmed milks was 8.29, 8.02, and 8.13, showing that the absorption of calcium depended on the growth of the organism, and not on a variation in the quantity ingested.

There is apparently a fixed and definite tendency toward uniform growth. Schapiro[2] found that if young kittens were chloroformed twice daily their growth was retarded in comparison with normal control animals. However, on stoppage of the chloroform treatment, the greater rapidity of growth during an after period fully compensated for the earlier delay in development. (See Chapter XIII, p. 375.)

Lusk has shown that if an amino-acid, such as alanin, be added to the diet of a dog there is a considerable stimulation of metabolism. (See p. 240.) Mendel, in unpublished experiments (cited here by permission), has demonstrated that the addition of alanin to the diet of growing rats has no influence whatever upon their rate of growth. Rubner[3] set forth

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[1] Calculated from Ostertag and Zuntz: "Landwirtsch. Jahrbücher," 1908, xxxvii, 211.

[2] Schapiro: Proceedings of the Physiological Society, "Journal of Physiology," 1905–6, xxxiii, p. xxxi.

[3] Rubner: "Archiv für Hygiene," 1908, lxvi, 43.

that the conditions which determine the "wear and tear" quota of protein metabolism and those which determine growth by the addition of a "growth quota" from protein in the diet, are entirely dissimilar, although without metabolism growth is impossible. Mendel's experiments show conclusively that the stimulation of the general metabolism itself in no way affects the fundamental capacity to grow.

Another instance which demonstrates that the young organism may grow in proportion to the energy ingested in the food is brought to light by calculations based on the work of E. Rost.[1] This author gave meat, fat, and bone-ash to three dogs of the same litter, the experiment starting on the ninety-eighth day of their lives and continuing eighty-eight days. The writer has thus calculated the results:

	Dog I.	Dog II.	Dog III.
Weight in grams at start	3,200	2,200	4,150
Weight in grams at end	6,280	4,640	8,750
Growth in grams	3,080	2,440	4,600
Growth in per cent	96	110	110
Available calories ingested	24,420	17,336	34,276
Gain in grams per 100 calories ingested	122	141	134

It is worthy of note that these growing dogs, fed with meat and fat, gained in weight nearly the same number of grams per 1000 calories ingested in the food. This law of growth seems reasonably established. It simply expresses the fact that during the normal development of the young of the same age and species a definite percentage of the food is retained for growth irrespective of the size of the individual.

Rubner,[2] in apparent ignorance of this work of Dr. Wilson, has arrived at essentially the same conclusions, and he finds that the law is true regarding all species (horse, calf, sheep, pig, dog, cat, rabbit) except man. He formulates the "law of constant energy expenditure" as follows: *The amount of*

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[1] Rost: "Arbeiten aus dem kaiserlichen Gesundheitsamte," 1901, xviii, 206.

[2] Rubner: "Das Problem der Lebensdauer und seiner Beziehung zu Wachstum und Ernährung," 1908.

energy (calories) which is necessary to double the weight of the newborn of all species (except man) is the same per kilogram no matter whether the animal grows quickly or slowly. To construct one kilogram of normal body substance containing 30 grams of nitrogen and 1722 calories, 4808 calories are required except in the case of man, where six times that amount is needed. This is almost in exact agreement with the experiments of Wilson.

The same principles apply to the growth of rats, as may be seen from the following, calculated from the results of Funk and Macallum,[1] who fed these animals during twenty-eight days:

	Normal.	Controls.	Stunted 20 Days.
Number of rats	2	2	2
Weight in grams at start	29	27.5	27.0
Growth in grams	40	42	65
Available calories ingested	1223	1216	1895
Gain in grams per 1000 calories ingested	32.7	34.5	34.3
Calories for construction of 1 gram new tissue	30.6	29.0	29.1

In the work of Hopkins[2] different sets of rats were given the same food in different quantities, and the following table has been calculated from the results obtained after nine days of food ingestion:

Number of rats used	12	14	18	15
Calories ingested daily per 100 grams of rats, live weight	45	50	55	60
Average initial weights, grams	45.3	45.2	42.2	43.2
Gain in grams of rats	8.8	10.3	11.1	12.8
Gain in grams per 1000 calories ingested	48	51	53	55

Another lot of rats when given 65 calories per hundred grams live weight refused to eat all their food. It is of great interest that, notwithstanding the restriction of the dietary below the limits set by the appetite in some of the experiments, yet the gain in the weight of the rats is nearly

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[1] Funk, C., and Macallum, A. Bruce: "Journal of Biological Chemistry," 1915, xxiii, 413.

[2] Hopkins: "Journal of Physiology," 1912, xliv, 425.

proportional to the calories in the dietary. Evidently, ample protein, together with calcium and other salts, was present for the construction of new tissue in all the rats. Aron[1] has shown that when growing dogs are given too little energy in their food, the skeleton may grow and the weight increase, though the caloric content of the animal may diminish.

Rubner finds in all species the constant retention of approximately the same percentage of the energy ingested, which averages 34.3 per cent., except in the case of man, where the energy retained for growth is only 5.2 per cent. He states that 40 per cent. of the energy ingested may be retained for the growth of pigs, whereas Dr. Wilson found only 20 per cent. so retained. This is because the pigs in the latter case were given skimmed milk, and the added tissue substance was found on analysis to have a heat value of only 866 calories per kilogram, instead of 1722 as assumed by Rubner.

It is therefore evident that while it requires the same energy equivalent to construct one kilogram of new substance in young animals, the percentage of energy retained for growth may depend upon the amount of fat in the diet.

Rubner states that if the requirement for energy in the various animals be placed at 100, then the amount of energy in the food actually ingested by them averages 202. This corresponds to Dr. Wilson's computation of the energy ingested by the growing pigs, which averaged 2100 calories per square meter of surface, as compared with a normal *requirement* of 1089. Dr. Wilson explained this high energy requirement as being partly due to growth and partly to the extreme activity of the little animals. A human infant does not require this large excess of energy in his food, probably because he is kept warm and sleeps much of the time.

Finally, Rubner has calculated that the quantity of energy metabolized in a kilogram of living cells from maturity to death is the same in different animals, except in the case of man, who again occupies an exceptional position.

[1] Aron: "Biochemische Zeitschrift," 1910–11, xxx, 207.

This is represented in the following table:

	Body Weight in Kg.	Length of Life in Years after Maturity.	Calories Produced per Kg. Adult Body Substance.
Man	60.	60	775,770
Horse	450.	30	169,900
Cow	450.	26	141,090
Dog	22.	9	163,900
Cat	3.	8	223,800
Guinea-pig	0.6	6	265,500

Rubner finds that among the animals each kilogram of adult body substance metabolizes an average of 191,600 calories and then dies. Man alone has power in his protoplasm to use a much larger share of energy in the furtherance of his activities.

Bunge[1] has recalled the relationship between rapidity of growth and longevity, as orginally suggested by Flourens in 1856. This writer believed that if the time of reaching the end of growth be multiplied by 5, the average term of life might be computed. This relationship may be tabulated as follows:

TABLE SHOWING FLOURENS' LAW OF LONGEVITY

	Time in Days from Birth to Double Birth-weight.	Time in Years Until Full Growth.	Deduced Average Longevity in Years.	Maximum Recorded Longevity in Years.
Man	180	20	90–100	152–169
Camel	. .	8	40	100
Horse	60	5	25	50
Cow	47	4	15–20	. .
Lion	. .	4	30	60
Cat	9½	1½	9–10	20
Dog	9	2	10–12	24

Bunge calls attention to the fact that a horse more often lives to be forty than a man to be a hundred. Either the law

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[1] Bunge: "Pflüger's Archiv," 1903, xcv, 606.

is false, or man is a too early victim of an improper heredity or environment.

Very little has been accomplished upon the subject of the mineral metabolism of growing children, so the following work of Jundell[1] is of especial interest. Two boys, K. and N., were given a diet during ten days containing 2.9 grams of protein, 2.7 grams of fat, 10.8 grams of carbohydrate, and in all 81 calories per kilogram of body weight daily. The mineral metabolism as calculated per kilogram of body weight daily was as follows:

MINERAL METABOLISM OF K. ($5\frac{1}{2}$ YEARS OLD, WEIGHT 18.4 KG.) AND OF N. ($7\frac{3}{4}$ YEARS OLD, WEIGHT 23.1 KG.) IN GRAMS PER KG. PER DAY

	INTAKE.		FECES.		URINE.		RETENTION.	
	K.	N.	K.	N.	K.	N.	K.	N.
Total ash	0.747	0.697	0.134	0.124	0.469	0.429	+0.144	+0.144
P_2O_5	0.144	0.136	0.049	0.043	0.064	0.064	+0.032	+0.030
CaO	0.060	0.076	0.050	0.042	0.007	0.045	+0.003	+0.029
MgO	0.071	0.065	0.047	0.041	0.010	0.008	+0.014	+0.016
K_2O	0.141	0.136	0.012	0.013	0.116	0.106	+0.012	+0.018
Na_2O	0.345	0.224	0.011	0.012	0.104	0.103	+0.231	+0.110
Cl	0.344	0.324	0.003	0.004	0.309	0.292	+0.032	+0.028

It may be calculated from this table that the older boy took 1.8 grams of calcium oxid in his food daily and retained about 0.07 gram. If the intake had been solely in the form of cows' milk, not far from a liter would have been required. One of the most important questions of the time concerns the determination of the quantity of salts in the food necessary to prevent malnutrition in children, and it would be well to know the quantity of cows' milk which should be prescribed in the daily diet of children in order to satisfy the mineral requirements for normal growth.

For metabolism in youth, see page 559.

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[1] Jundell: "Nordiskt Medicinskt Arkiv," 1914, xlvii, Abth. 2, 1.

CHAPTER XV.

METABOLISM IN ANEMIA, AT HIGH ALTITUDES, IN MYXEDEMA, AND IN EXOPHTHALMIC GOITER

In man one-thirteenth part of the body weight is carried as blood to the lungs at least every minute and there exposed for a period of two seconds to the action of the alveolar air. The blood in the capillaries of the lungs may be estimated as a film 0.01 millimeter in thickness and 150 square meters in area, or nearly a hundred times the area of the surface of the body. Zuntz estimates the combined thickness of the alveolar wall and capillary wall at 0.004 mm. This is the total distance separating the alveolar air from the blood. The gaseous exchange between air and blood is thus readily made possible.

In an experiment by Henriques[1] four different determinations were made upon an anesthetized dog: (1) The rate of flow of blood; (2) the carbon dioxid and oxygen content of the venous blood in the right heart; (3) the quantity of the same gases in the blood of the femoral artery, that is, after the lungs had been traversed, and (4) the extent of the gaseous exchange in the lungs was measured. The rapidity of the blood flow was 1806 c.c. in three minutes. The following calculations show that no oxidation took place in the lungs or in the blood, and in publishing these results Henriques recants a contrary opinion previously held by him:

	CO_2. C.C.	O_2. C.C.	R. Q.
In 100 c.c. blood of right heart	44.34	2.74	
In 100 c.c. blood of femoral artery	31.55	15.25	
Difference	−12.79	+12.51	
Calculated from 1806 c.c. blood flow	231	226	1.02
Respiration experiment (three minutes)	250	239	1.05
Difference	8 per cent.	5 per cent.	

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[1] Henriques: "Biochemische Zeitschrift," 1915, lxxi, 481.

The differences are within the limits of experimental error. It is evident that the place of oxidation is in the tissues (see p. 32).

Complete deprivation of oxygen results in asphyxiation and death. The question arises, Will there be any effect upon metabolism if the oxygen supply for the body be reduced? Such a reduction of oxygen available for the tissues might be brought about by bloodletting, anemia, carbon-monoxid poisoning, by life on high mountains, or in balloons at high altitudes, or in pneumatic cabinets at reduced pressure, or by the artificial restriction of the free influx of atmospheric air into the lungs. Any of these methods if carried beyond a certain point is known to produce death.

It was noted by Lavoisier and confirmed by Regnault and Reiset that the respiration of pure oxygen did not increase the metabolism. Liebig was convinced that atmospheric pressure was without influence, for it was evident to him that life at the sea-level was of the same character as on high mountains. In confirmation of these principles Zuntz[1] has definitely shown that if air rich in oxygen be respired, there is an increased oxygen absorption lasting for about one minute, and then the normal quantity is absorbed. The primary increase in the quantity of oxygen absorbed is due to the filling of the lungs with oxygen and a further saturation of the blood with it, processes which are without effect on tissue metabolism. There is apparently no retention of such oxygen within the cells of the organism.

However, Hill and Flack[2] show that in the fatigue of athletes oxygen inhalation increases the lasting power and decreases the fatigue, probably by maintaining or restoring the vigor of the heart. They believe that the fatigue which follows an athletic feat is mainly cardiac in origin and due to want of oxygen.

Pflüger[3] first showed that frogs could live for a long period in an atmosphere which was free from oxygen when they were maintained at a temperature of 0°. After five hours they

[1] Zuntz: "Archiv für Physiologie," 1903, Suppl., p. 492.

[2] Hill and Flack: "Journal of Physiology," 1909, xxxviii, p. xxviii.

[3] Pflüger: "Pflüger's Archiv," 1875, x, 313.

were capable of movement, and after seventeen hours, although apparently dead, they could be revived when placed in the air. Fletcher and Hopkins[1] have found traces of lactic acid in normal resting frog's muscle, and also traces after a series of muscular contractions which were induced in an atmosphere of oxygen; but they found lactic acid in large quantity in the muscle if the contractions were brought about under anaërobic conditions.

Lesser[2] has placed frogs in an ice calorimeter and filled the chamber in which they lived first with air and then with hydrogen. When living in air the animals produced more heat and only half as much carbon dioxid as they did when they lived in hydrogen gas. In the air each milligram of carbon dioxid exhaled corresponded to a production of 4.5 small calories; in hydrogen, to only 1.6 calories. Hence the processes taking place in the two cases could not have been the same. The anaërobic carbon dioxid production could not have been at the expense of oxygen stored in the tissues of the frog or the heat production per unit of carbon dioxid exhaled would have been the same as in air, instead of being only 35 per cent. as much. The processes involved in this case can only be conjectured. It has already been stated that *ascaris*, an anaërobic inhabitant of the intestine, may convert glycogen into fatty acid with the elimination of carbon dioxid and the evolution of heat. (See p. 305.) Similar processes might take place in the anaërobic frog.

Lesser[3] has further shown that the quantity of oxygen absorbed by a frog at 15° is independent of the pressure of oxygen in the atmosphere until a percentage of 3.3 of oxygen is reached. At this point the respiratory quotient was 1.02. When 1.8 per cent. of oxygen was present the quantity of oxygen absorbed decreased to one-third the normal and the respiratory quotient rose to 2.40, indicating anaërobic cleavage of the food materials with the production of carbon

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[1] Fletcher and Hopkins: "Journal of Physiology," 1907, xxxv, 247.

[2] Lesser: "Zeitschrift für Biologie," 1908, li, 287.

[3] Lesser: "Biochemische Zeitschrift," 1914, lxv, 400.

dioxid. After eight hours of this treatment the frog became paralyzed.

According to Zuntz,[1] any anemic condition which results in the production of lactic acid makes demands on the glycogen reserves of the body, so that sugar may rise abnormally in the blood, and both sugar and lactic acid appear in the urine.

Muscular exertion in man leads to an increase in the quantity of lactic acid in both blood[2] and urine,[3] due, in all probability, to slight local anemia in the muscles. (See p. 322.)

The consideration of the subject of subnormal oxygen supply may first be considered in connection with bloodletting, which produces an artificial anemia. Bauer,[4] in Voit's laboratory, was the first to study this systematically, and found that the immediate result of bloodletting in the dog was an increased protein metabolism, but that the carbon dioxid elimination was unchanged; 18 to 27 per cent. of the total blood in the body was removed in these experiments.

Hawk and Gies[5] confirm the reports of a higher protein metabolism after bloodletting.

Finkler,[6] in Pflüger's laboratory, withdrew one-third of the total blood from a dog, thereby reducing the rapidity of bloodflow in the femoral artery by one-half, and yet there was no change in the quantity of oxygen absorbed, and, therefore, of the quantity of the carbon dioxid exhaled. Finkler noted, however, that the quantity of oxygen in the venous blood grew constantly less after repeated bleedings. This indicates the interrelation between the oxygen supply and the needs of the tissues. Under ordinary circumstances there are 20 volumes per cent. of oxygen in the arterial blood, of which 12 volumes per cent. may return as an unused excess to the right heart.

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[1] Zuntz: "Die Kraftleistung des Tierkörpers," Festrede, Berlin, 1908, p. 18.

[2] Fries: "Biochemische Zeitschrift," 1911, xxxv, 368.

[3] Spiro: "Zeitschrift für physiologische Chemie," 1877, i, 111; Ryffel: "Journal of Physiology," 1909–10, xxxix, p. xxix.

[4] Bauer: "Zeitschrift für Biologie," 1872, viii, 567.

[5] Hawk and Gies: "American Journal of Physiology," 1904, xi, 226.

[6] Finkler: "Pflüger's Archiv," 1875, x, 368.

Repeated bleedings by Finkler reduced this percentage in venous blood from 11.80 per cent. to 8.80, 4.06, and 2.71 per cent. The carbon dioxid content of the blood remained unchanged. This decrease in the oxygen content of the blood may stimulate both the heart and respiration to compensatory activity, although nothing resembling asphyxia be present. While the total heat production is unchanged in anemia following bloodletting (except as influenced by increased cardiac and respiratory activity), still it is evident from the diminution of oxygen present in venous blood that there would not be a sufficient supply of oxygen to provide for a largely increased metabolism. Hence the anemic organism is incapable of great muscular work without quick exhaustion accompanied by rapid respiration and heart-beat. These latter are further efforts of compensation for the decrease in the oxygen-carrying elements of the blood.

The removal of blood from a dog, followed by the transfusion of an equal quantity, has no effect upon metabolism,[1] although if an artificial plethora be induced by the intravenous injection of fresh blood into a normal animal, the metabolism is slightly increased, a result which is probably due to increased heart action.[2]

After bloodletting of any considerable magnitude, lactic acid and, it is reported, a small amount of sugar appear in the urine. Thus Araki[3] found lactic acid in the urine of rabbits which had been bled. He also found lactic acid in the urine of rabbits which had been exposed to the action of rarefied air, and he found lactic acid and glucose in the urine of animals the oxygen-carrying capacity of whose blood had been diminished through the respiration of carbon monoxid. It should be noticed in passing that wherever lactic acid is formed in the organism there is a concomitant rise in protein metabolism. Since this lactic acid is a derivative of glucose, its non-combustion may raise the protein metabolism to a

[1] Pembrey and Gürber: "Journal of Physiology," 1894, xv, 449.

[2] Hári: "Biochemische Zeitschrift," 1911, xxxiv, 111; 1912, xliv, 1.

[3] Araki: "Zeitschrift für physiologische Chemie," 1894, xix, 424

higher level, just as is the case when sugar remains unburned in diabetes.

In experimental anemias the hemoglobin content of the blood of rabbits[1] or dogs[2] may be reduced to 20 per cent. of the normal amount, with indications of only slight changes in the intensity of the oxidative processes, and these are usually in the direction of slight increases. Such increases one may interpret as being derived from the rise in protein metabolism and as due to stimulation of the cells by lactic acid (see p. 298).

Another fact which has been observed by Lewinstein[3] is that when rabbits are kept in a bell-jar at a barometric pressure of 300 to 400 mm. (corresponding to 5000 to 7500 meters above sea-level) they die on the second or third day, and autopsy reveals extreme fatty infiltration of heart, liver, kidney, and diaphragm. These animals took no food. The cause of this fatty change, in the present writer's opinion, was the lessened combustion of sugar or its derivative, lactic acid, which always induces an abnormal deposit of fat in any sugar-hungry cells (p. 490).

Köhler[4] artificially compressed the trachea of rabbits by tying a lead wire around it. The animals recovered from the operation and lived for four weeks in a condition of dyspnea. Appetite, weight, urine, and body temperature remained normal almost until the end. The dyspnea was apparently insufficient to affect the metabolism. Increased respiration and heart activity were effectual efforts at compensation, so that there was no lack of oxygen in the animals. However, the altered pressure in the lungs and the continued dyspnea brought about a condition of stasis of which the animal died. The secondary alterations were acute and wide-spread, and were hyperemia of the lungs, vesicular and intralobular emphysema of the lungs, and hypertrophy of both sides of the heart.

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[1] Eberstadt: "Archiv für exp. Path. und Pharm.," 1913, lxxi, 329.

[2] Rolly: "Deutsches Archiv für klinische Medizin," 1914, cxiv, 605.

[3] Lewinstein: "Pflüger's Archiv," 1897, lxv, 278.

[4] Köhler: "Archiv für exp. Path. und Pharm.," 1877, vii, 1.

Pettenkofer and Voit[1] observed the metabolism in an acute case of leukocythemia of four years' duration, and at a time four months before the death of the patient. There was one white to every three red blood-corpuscles, a high degree of anemia, and great physical weakness. The metabolism was exactly the same as in a normal resting man living under the same dietary conditions.

Magnus-Levy states that, rightly interpreted, these experiments of Voit indicate an increased metabolism. He[2] found an increased metabolism in a case of severe pernicious anemia. Grafe[3] reports a large increase in metabolism in leukemia. Rolly,[4] however, states that in chlorosis and in mild anemias there is no increase in metabolism in human beings.

Meyer and Du Bois[5] made calorimetric observations upon 5 patients suffering from anemia. Direct and indirect calorimetry agreed within 3 per cent. and the respiratory quotients ranged within the normal limits. The following table epitomizes their results:

METABOLISM IN ANEMIA IN MAN

	Type.	Hemoglobin in Blood in Per Cent.	Increase in Heat Production Above Basal in Per Cent.
Case I.	Splenic	25	8
Case II.	Pernicious	20	24–19
Case III.	Pernicious: transverse myelitis	23–21	33–7
Case IV.	Pernicious	44	2
Case V.	Pernicious	40	6

These results show an increased metabolism in pernicious anemia which is especially pronounced when the hemoglobin content of the blood falls to 20 per cent. of the normal.

In Case III the legs were wasted and atrophic and could no

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[1] Pettenkofer and Voit: "Zeitschrift für Biologie," 1869, v, 319.

[2] Magnus-Levy: "Zeitschrift für klinische Medizin," 1906, lx, 179.

[3] Grafe: "Deutsches Archiv für klinische Medizin," 1911, cii, 406.

[4] Rolly: *Loc. cit.*

[5] Meyer, A. L., and Du Bois: "Archives of Internal Medicine," 1916, xvii, 965.

longer be used. Of itself, this condition would have lowered the metabolism.

Meyer calculated for Case II that there were 3.7 c.c. of oxygen in 100 c.c. of arterial blood. If the patient had had a normal heart-beat of 70 per minute with an output of blood of 50 c.c. per beat, 130 c.c. of oxygen would have been carried to the tissues per minute. In fact, 252 c.c. of oxygen were absorbed by the patient each minute and his pulse-rate was 101. To have supplied enough oxygen for tissue respiration his output of blood per heart-beat must have been at least 66 c.c.

Another patient with lymphatic leukemia had a very high metabolism which was scarcely affected by vigorous *x*-ray therapy, although the lymphocytes were greatly diminished in number.[1]

The characteristic optical properties of human hemoglobin, its power to combine with between 1.33 to 1.35 c.c. of carbon monoxid gas per gram of substance, and its iron content of 0.33 to 0.34 per cent., are always constant, both normally and in diseases such as polycythemia, pernicious anemia, chlorosis, scurvy, and pseudoleukemia. This important fact, which shows that hemoglobin is not itself chemically changed in anemia, was demonstrated by Butterfield.[2]

In emphysema of the lungs in man determinations by Geppert and by Speck[3] have shown that the respiratory exchange of gases was entirely within normal limits.

Carpenter and Benedict[4] have found the metabolism of a man in whom the left lung was entirely obliterated to be unchanged from the normal.

It is evident from these various citations that the general oxidation of the body is normally maintained in anemia and in pulmonary disease, provided the disturbances are not of extreme intensity.

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[1] Means and Aub, unpublished.

[2] Butterfield: "Zeitschrift für physiologische Chemie," 1909, lxii, 173.

[3] Cited by Jaquet: "Ergebnisse der Physiologie," 1903, ii, I, 562.

[4] Carpenter and Benedict: "Journal of Biological Chemistry," 1909, vi, p. xv.

The constantly increasing use of mountain air as a recuperative force for the worn-out individual leads to the inquiry whether the metabolism at high altitudes is different from that at the sea-level. For knowledge of this sort we are principally indebted to Zuntz and his pupils. The study of the subject may be taken up by using three different methods: First, the pneumatic cabinet; second, balloon ascensions; third, mountain ascents.

The pressure of the atmosphere varies with the height from the sea-level as appears in the following table:

Altitude.			Barometer in Mm. Hg.
Meters.	Feet.	Miles.	
0	0	0.	760
1000	3,281	0.6	670
2000	6,562	1.2	592
3000	9,843	1.9	522
4000	13,124	2.5	460
5000	16,405	3.1	406
6000	19,686	3.7	358
7000	22,967	4.4	316
8000	26,248	5.0	297
9000	29,529	5.6	

In a celebrated balloon ascension made by Tissandier and two companions in 1875 only Tissandier lived to tell the following tale:

At a height of 7000 meters Tissandier is unable to make the effort to remove his gloves from his pocket. All breathe oxygen. The temperature is −11°. Sivel throws ballast. At 7500 meters the condition of torpor is extraordinary, but there is no suffering. The arms cannot be moved to reach for the oxygen tube. At 280 mm. barometric pressure Tissandier wishes to call out that the level of 8000 meters has been passed, but cannot speak. Consciousness is then lost. The height of 263 mm. barometric pressure is reached before the balloon begins to descend and, on recovery of consciousness, Tissandier finds that his two companions are dead.

In 1909 the Duke of Abruzzi, with several companions, ascended to a height of 7500 meters (= 24,600 ft, = 4.7 miles = 312 mm. Hg.) in the Himalayas, and although the physical conditions were extremely trying, they suffered no serious physiologic inconvenience. Douglas, Haldane, Henderson, and Schneider[1] point out that this immunity was acquired by prior acclimatization during two months of residence at an altitude of 17,000 feet. The ascent of Mt. Everest, the highest mountain in the world (8840 meters = 29,000 feet = 5.5 miles), though perhaps physically unattainable, may not be physiologically impossible.

The relative composition of the atmosphere is the same at all distances from the earth's surface. Durig and Zuntz[2] find that the atmosphere at a height of 2900 meters contains carbon dioxid 0.03 per cent., nitrogen 79.11 per cent., and oxygen 20.86 per cent., whereas at an altidude of 4600 meters it contains carbon dioxid 0.03 per cent., nitrogen 79.10 per cent., oxygen 20.87 per cent. These are values practically identical with each other and with those determined at sea-level.

Fraenkel and Geppert[3] placed a dog which had fasted seven days under the influence of greatly diminished atmospheric pressure and found an increased protein metabolism which continued on the second and third days. They also suspected the presence of products of incomplete combustion in the urine. These results accord with Araki's investigations.

Von Terray[4] finds no change in the respiratory activity of dogs in air containing between 87 and 10.5 per cent. of oxygen. When 10.5 per cent. of oxygen is present an increased respiratory activity commences. With 5.25 per cent. of oxygen there is every indication of lack of oxygen for the tissues, and the elimination of lactic acid in the urine is pronounced. The quantity of lactic acid eliminated was greatest after the respiration of an atmosphere containing 3 per cent. of oxygen. The quantities obtained were 1.206, 1.860, 2.176, 2.300, 2.352, 2.663, 3.020, and 3.686 grams of lactic acid in twenty-four

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[1] Douglas, Haldane, Henderson, and Schneider: "Transactions of the Royal Society," 1912, Series B, cciii, 185.

[2] Durig and Zuntz: "Archiv für Physiologie," 1904, Suppl., p. 421.

[3] Fraenkel and Geppert: "Ueber die Wirkungen der verdünnten Luft," 1883.

[4] von Terray: "Pflüger's Archiv," 1896, lxv, 440.

hours. In these cases we again see the analogy of the metabolism to that already cited as having been discovered by Araki after bloodletting in rabbits.

L. Zuntz[1] found that when he respired in a pneumatic cabinet at an atmospheric pressure of 448 mm. of mercury there was no change in his respiratory metabolism as compared with the normal. The results may be tabulated as follows:

Per Cent. O_2 in Air.	Pressure in Mm. Hg.	Respired per Minute. O_2 C.C.	CO_2 in C.C.
21	758 mm.	231.25	200.15
12	448 mm.	238.7	213.1

This latter experiment was done at a pressure corresponding to a mountain height of 4500 meters. He also showed that variations in atmospheric pressure within the above limits had no effect on the metabolism during muscular exercise.

This work was repeated by Hasselbalch and Lindhard[2] in an experiment which lasted twenty-six days. During fourteen days a man remained in a pneumatic cabinet at an atmospheric pressure of 455 mm. The consumption of oxygen and the urinary ammonia and amino-acids were unaffected by this influence.

Von Schrötter and Zuntz[3] made two balloon ascents to heights of 4560 and 5160 meters. Zuntz showed an increased oxygen absorption of 7 per cent. above that at sea-level. In the case of Von Schrötter the increase was slight except during one interval of shivering, when a 20 per cent. increase was recorded. The authors attributed the slight rise in the metabolism to the increased work done by the respiratory muscles. During the higher ascent sugar appeared in the urine of Zuntz, indicating incomplete oxidation.

A research of Zuntz[4] on the subject of mountaineering describes how he and Durig ascended to the Col d'Olen (2900 meters), and, having remained there for a week, passed up-

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[1] Loewy and Zuntz: "Pflüger's Archiv," 1897, lxvi, 477.

[2] Hasselbalch and Lindhard: "Biochemische Zeitschrift," 1914, lxviii, 265 and 295.

[3] von Schrötter and Zuntz: "Pflüger's Archiv," 1902, xcii, 479.

[4] Durig and Zuntz: "Archiv für Physiologie," 1904, Suppl., p. 417.

ward to a hut (4560 meters) constructed near the summit of Monte Rosa, the highest mountain of the Alps after Mont Blanc. They lived in this hut two weeks and a half. The height of the barometer was 443 millimeters, which indicates a quantity of oxygen amounting to 12.2 per cent. of an atmosphere. On the Col d'Olen there was no increase in their metabolism when they were resting, and there was no increase in the requirement of energy necessary to accomplish one kilogrammeter of work. This agrees with the results of Bürgi elsewhere mentioned (p. 332). At the higher level, near the summit of the mountain, the resting metabolism increased at once and permanently to the extent of 15 per cent. Zuntz during a former sojourn had noted an increase of 44 per cent. in his metabolism when on the mountain. Exposure to the sunlight was almost without effect on the metabolism. The increased metabolism was not due to cold, for it was present when the individual was in a warm bed in the hut. At sea-level the energy equivalent of 3 kilogrammeters is liberated in the body in order to lift 1 kilogram of body substance 1 meter high. Here on the snow-fields of Monte Rosa Durig required the equivalent of 4.0 to 4.8, Zuntz 5.3 to 6.8 kilogrammeters of energy to accomplish 1 kilogrammeter of work. This agrees with a former experiment of Zuntz when he was living in the same locality, in which he found the increased metabolism necessary to effect 1 kilogrammeter of work in climbing was 70 per cent. above the requirement for the same work at sea-level.

Hasselbalch and Lindhard,[1] while noting that the ultraviolet rays of the sun reduce the frequency and increase the depth of respiration, find that exposure to the effect of such rays in the high Alps (Brandenburger Hut, 3290 meters) has no effect upon the metabolism (see p. 150).

Not only is the metabolism necessary to accomplish work greater on high mountains than at sea-level, but the capacity

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[1] Hasselbalch and Lindhard: "Skan. Archiv für Physiologie," 1911, xxv, 361.

for work is greatly reduced. Schumburg[1] found that he could accomplish a maximum of 999 kilogrammeters of work in one minute in Berlin, 619 when on the Monte Rosa glacier, and only 354 kilogrammeters when he was on the top of the mountain. The limit of work on Monte Rosa was, therefore, one-third what could be accomplished in Berlin, probably on account of the accumulation of imperfectly oxidized products of metabolism, which reduces the muscular power.[2]

Durig and Zuntz, Mosso, and others have found their respiration to be distinctly of the Cheyne-Stokes character after a return to the hut subsequent to exercise in the higher Alps. They found that when they were on Monte Rosa a temporary oppression resulted if their respiration was partly hindered—as in the case of lacing their boots. Also strict attention to a definite task might reduce the respiratory activity to such an extent that anemia of the brain, accompanied by dizziness, readily ensued.

In 1911 the Anglo-American Pike's Peak Expedition, consisting of Douglas, Haldane, Yandell Henderson, and Schneider,[3] spent several weeks on the summit of Pike's Peak with a view to making a thorough study of physiologic adaptation to low atmospheric pressures. The altitude of Pike's Peak is 4290 meters (14,100 feet), which contrasts with the altitude of 4560 meters at which the laboratory on Monte Rosa is located. Pike's Peak, however, differs from Monte Rosa in having a summit which in summer time is almost free from snow, in facility of access by means of a cogwheel railway and in the possession of a very comfortable hotel. The distance from Manitou to the summit is 16.3 kilometers (8.9 miles) by the cog-railway and the difference in altitude between the two localities is 2220 meters (7485 feet). Robinson, the resident manager of the hotel, has resided six months each year for

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[1] Schumburg and Zuntz: "Pflüger's Archiv," 1896, lxiii, 488.

[2] Lee: Fatigue, "The Harvey Lectures," 1905–06, p. 169.

[3] Douglas, Haldane, Henderson, and Schneider: "Transactions of the Royal Society," 1912, Series B, cciii, 185.

seventeen years on the summit and holds the record for the most rapid ascent of the peak, having accomplished it in two hours and thirty-one minutes. This means walking at the rate of 6.5 kilometers (3.5 miles) per hour and ascending at the rate of 906 meters (2974 feet) during the same interval. Since the body weight was 70 kilograms the hourly heat production might have been (see p. 327):

	KGM.	CALORIES.
For lifting the body weight (70 × 906 × 3)........	190,260	447
For horizontal forward movement (70 × 0.217 × 6500)....................................	98,735	232
	288,995	679
Add for metabolism standing at rest..............	....	88
		767

The requirement of 767 calories per hour exceeds that needed by the trained bicycle rider who rides until exhausted. (See p. 321.)

Contrary to the observations of the Zuntz school, the members of the Pike's Peak Expedition found no difference in their metabolism on the summit of Pike's Peak from that at sea-level, either during rest or when taking exercise such as walking at the rate of one to five miles per hour. These results were obtained after acclimatization, and this may account for the difference from those obtained on Monte Rosa.

The ventilation of the lungs of Durig and Zuntz while at rest at different altitudes varied as follows:

	RESPIRED IN LITERS PER MINUTE.		
	Zuntz. Actual.	Zuntz. Reduced to 760 Mm. Hg and 0° C.	Durig. Reduced to 760 Mm. Hg and 0° C.
Sea-level......	4.61–5.03	4.15–4.53	5.00–5.63
Col d'Olen....	5.97–6.36	3.99–4.16	3.81–5.07
Monte Rosa...	6.86–8.52	3.71–4.88	4.05–4.60

The actual amount of inspired air appears to be about the same at different altitudes, an increased volume compensating for increasing rarefaction of the atmosphere.

The atmosphere in which one lives is really the air within the alveoli (Pflüger). Durig and Zuntz have calculated the pressure of oxygen and carbon dioxid within their alveoli at different levels, and, measured in terms of millimeters of mercury, have found them to be as follows:

	Pressures in Mm. Hg.			
	Zuntz (of Berlin).		Durig (of Vienna).	
	O_2	CO_2	O_2	CO_2
At home—rest	107	36	109	32
At home—ascending walk	109	33	99	37
On Monte Rosa—rest	57	21	53	24
On Monte Rosa—horizontal walk	60	17	55	21
On Monte Rosa—ascending walk	63	18	55	24

It is evident from a study of the results that muscular exercise in all these localities produces an increase in the alveolar tension of oxygen and a decrease in that of carbon dioxid. This is brought about by the stimulation of respiration.

It will be interesting to examine the evidence of the effect of decreasing oxygen tension on the capacity of the blood in the lungs to absorb oxygen. The usually accepted doctrine that atmospheric air, shaken with blood, will practically saturate the hemoglobin present, rests upon Hüfner's experiments with carefully prepared solutions of hemoglobin. Loewy and Zuntz,[1] however, show that if normal blood be used the saturation is 89 per cent. at the most. On the basis of this newer work, Durig and Zuntz[2] have calculated the saturation of the hemoglobin within the blood at the different altitudes. At Berlin, oxygen exerting alveolar pressures of 113 and 103 mm. would saturate the blood in the lungs to the extent of 81.9 and 80.5 per cent. respectively. On Monte Rosa alveolar oxygen at pressures of 57 mm. (Zuntz) and 53.2 mm. (Durig) would

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[1] Loewy and Zuntz: "Archiv für Physiologie," 1904, p. 207.

[2] Durig and Zuntz: *Loc. cit.*, p. 442.

respectively cause a saturation to the extent of 69.5 and 68 per cent. The lowest recorded oxygen pressure in the alveoli was 48.3 mm. (Durig), which corresponded to 65.9 per cent. of oxyhemoglobin, and was accompanied by severe headache. A quickened heart-beat produced a more rapid circulation than normal. The experimenters find no ground for believing that there was at any time any real oxygen deficiency in any of the important tissues of the body. They consider that their gradual ascent from sea-level prevented the usual disturbances of appetite and digestion which are probably caused by anemia in the abdominal region (mountain sickness).

Lactic acid has been found in increased amounts in the blood of individuals on high mountains.[1] Acidosis quickens the respiration and lowers the carbon dioxid content of the blood and raises the oxygen pressure in the lungs (see p. 218). In mountain sickness the body temperature may rise as high as 42° C.,[2] a temperature which favors the free dissociation of oxyhemoglobin.[3]

Boycott and Haldane[4] found in experiments on themselves when they were confined in a steel pneumatic cabinet that if the atmospheric pressure was reduced to 356 mm. of mercury, corresponding to a height of 6000 meters (= 20,000 feet) the oxygen pressure in the alveoli fell to 30 mm. and pronounced cyanosis occurred, accompanied first by loss of memory and then by unconsciousness. There was only slight hyperpnea. Greater attenuation of the atmosphere on mountains and in balloons may often be tolerated. This they ascribe to a gradual production of lactic acid within the organism which renders the respiratory center especially sensitive to the stimulus of carbon dioxid. They recommend that one frequently partake of carbohydrates when among the higher mountains in order that a maximum amount of carbon dioxid be furnished to the blood-stream. The carbon dioxid pressure in the alveoli

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[1] Galeotti: "Arch. ital. de Biologie," 1904, xli, 80.

[2] Caspari and Loewy: "Biochemische Zeitschrift," 1910, xxvii, 405.

[3] Barcroft and King: "Journal of Physiology," 1909–10, xxxix, 374.

[4] Boycott and Haldane: *Ibid.*, 1908, xxxvii, 355.

falls as an accompaniment of the rising acid content of the body. This changed condition of the blood does not pass off at once on return to a lower level.[1] The respiratory stimulus persists and the beneficial effects of descending are promptly felt. At a given altitude on the descent the alveolar oxygen pressure will therefore probably be higher than at the same altitude on the ascent on account of the greater stimulation of the respiratory center.

These relations are shown in the following table compiled from Ward's experiments on himself:

	Pressures in Mm. of Hg.		
	Barometer.	Alveolar Air.	
		CO_2.	O_2.
Lister Institute, London	769	37.7	109.0
Zermatt	633	34.2	81.6
Monte Rosa	443	28.5	49.8
Zermatt, on return	633	28.9	91.0
Two hours after	...	32.5	

One may compare the statement of Boycott and Haldane that cyanosis occurred in them when the oxygen pressure in the alveoli fell to 30 mm. with the statement of Loewy and Zuntz[2] that when the oxygen pressure is 31.8 human blood will absorb oxygen so that 56 per cent. of its hemoglobin is saturated. This agrees well with the finding of Ringer[3] in the author's laboratory that dogs lose consciousness when their hemoglobin becomes half-saturated with carbon monoxid gas. Ringer's dogs, however, were not beyond the power of resuscitation until 70 per cent. of the hemoglobin was combined with the poisonous gas.

This observation is similar to that of Bornstein and Müller,[4]

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[1] Ward: "Journal of Physiology," 1908, xxxvii, 378.

[2] Loewy and Zuntz: "Archiv für Physiologie," 1904, p. 214.

[3] Ringer: Unpublished.

[4] Bornstein and Müller: "Archiv für Physiologie," 1907, p. 470.

who have shown that death occurs when 70 per cent. of the hemoglobin of the blood is converted into methemoglobin by magnesium chlorid. Rapid recovery takes place if the process is not carried so far as this.

The discovery of Viault[1] that at an altitude of 4000 meters the number of red blood-cells increased to 7,000,000 and 8,000,000 per cubic mm. of blood appeared at first to indicate a compensatory increase in oxygen-combining power during life in rarefied air. An increase in the quantity of hemoglobin has been positively shown by Zuntz and his coworkers.[2]

While in the high altitudes of Monte Rosa, von Wendt[3] noticed a retention of nitrogen, iron, and potassium which he suggests was in part used for the construction of new red blood-corpuscles, in part for the upbuilding of new musculature.

The Pike's Peak Expedition already referred to does not fully agree with the interpretations of the Zuntz school. The numerous visitors who reached the summit of Pike's Peak by train and remained only about three-quarters of an hour showed blueness of the lips and cheeks, accompanied by great hyperpnea on exertion. Only a few became miserable and faint and required oxygen for their restoration. Among those who arrived on foot, frequently after ten hours of effort, the symptoms were much more severe: nausea, vomiting, headache, and fainting being common. The nose-bleed traditionally assigned as characteristic of life in rarefied atmospheres is mythical. The process of acclimatization follows these lines: (1) The production of acids which reduce the alkalinity of the blood, this in turn stimulating the respiratory center with a resultant increase in ventilation of the lungs, a fall in the alveolar carbon dioxid tension and an increase in the oxygen tension; (2) an increase up to 150 per cent. of the normal amount of

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[1] Viault: "Comptes rendus de l'académie des sciences," 1890, cxi, 917.

[2] Zuntz, Loewy, Müller, and Caspari: "Höhenklima und Bergwanderungen in ihrer Wirkung auf den Menschen," Berlin, 1906.

[3] von Wendt: "Skan. Archiv für Physiologie," 1911, xxiv, 247.

hemoglobin. These factors are of such influence that even more than the normal quantity of oxygen may be carried to the tissues. The hemoglobin was found to be saturated with oxygen to an extent of 95 per cent., which is contrary to the teachings of Zuntz. The authors believe that only adherence to the theory that the alveolar epithelium secretes oxygen from the air into the blood will explain this phenomenon. The pulse and blood-pressure were but little affected. On passing from the summit of the mountain to the sea-level a fortnight is required before the stimulus to the respiratory center disappears and the alveolar carbon dioxid tension becomes normal, and several weeks pass before the total quantity of hemoglobin in the body returns to the normal. It is evident that in unacclimated persons balloon ascents and the like are to a greater extent dangerous to life than in those who have undergone climatic adaptation to high altitudes. Into all phases of the fascinating work of the Pike's Peak Expedition it is impossible to go.

The work was ably supplemented by that of Miss Fitzgerald,[1] who worked among acclimated mine attendants and their wives, persons who had lived a year or more at different heights above the sea-level in Colorado, some of them having been born in these localities. The records included, among others, some made at Denver (5100 ft.), Colorado Springs (6000 ft.), Cripple Creek (10,000 ft.), Camp Bird Mine (11,300 ft.), Lewis (12,500 ft.), and Pike's Peak (14,100 ft.). Miss Fitzgerald showed that for every 100 mm. fall in barometric pressure there was an increase of 10 per cent. above the amount of hemoglobin present in the body at the level of the sea, the law holding true for both sexes. Also, for every fall of 100 mm. in the atmospheric pressure there is a fall of 4.2 mm. in the pressure of alveolar carbon dioxid, accompanied by a progressive fall in the oxygen pressure.

From the facts she makes the following computation:

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[1] Fitzgerald: "Transactions of the Royal Society of London," 1913, Series B, cciii, 351.

TABLE SHOWING THE TENSION OF THE ALVEOLAR GASES IN ACCLIMATED INDIVIDUALS

Approximate Altitude When Mean Temperature of Air Column = 15° C.		Atmospheric Pressure.	Alveolar Air.			
			Percentage.		Partial Pressure.	
Meters.	Feet.		O_2.	CO_2.	O_2.	CO_2.
		Mm.			Mm.	Mm.
Sea-level.	Sea-level.	760	14.33	5.58	102.2	39.8
122	400	750	14.26	5.59	100.0	39.2
698	2,290	700	14.17	6.66	92.9	37.1
1326	4,350	650	14.01	5.80	84.5	35.0
2004	6,578	600	13.83	5.95	76.5	32.9
2743	8,999	550	13.62	6.12	68.5	30.8
3552	11,653	500	13.36	6.34	60.5	28.7
4447	14,589	450	13.05	6.60	52.6	26.6
5445	17,864	400	12.64	6.94	44.6	24.5
6579	21,584	350	12.10	7.39	36.7	22.4
7889	25,882	300	11.34	8.02	28.7	20.3
9437	30,960	250	10.24	8.97	20.8	18.2

Each successive diminution of 100 c.c. of barometric pressure causes a greater absolute increase in the ventilation of the lung and this introduces more oxygen. The full reaction, however, is not effected in short periods. Thus, in the experiment by Boycott and Haldane (see p. 433) in which they subjected themselves to a barometric pressure of 350 mm., their alveolar carbon dioxid tensions were 31.2 and 27.3 mm. respectively. In an acclimatized individual the carbon dioxid tension at this level of the barometer would have been 22.4 mm. and he would have had 3.2 per cent. more oxygen in his alveoli than Haldane had. Acclimatization involving this reaction, as well as increasing the quantity of hemoglobin, would have prevented the cyanosis and unconsciousness which followed in the experiments of Boycott and Haldane when they were in the respiration chamber.

Durig and Zuntz[1] made a voyage to Teneriffe, one of the Canary Islands (situated at about the latitude of Florida), and there ascended a volcano which rises to a height of 3160

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[1] Durig and Zuntz: "Biochemische Zeitschrift," 1912, xxxix, 435.

meters. They found no essential difference in their metabolism from that at Col d'Olen (2865 meters) except a slight increase due to a quickened rate of respiration which they ascribed to the effect of sunlight.

The results of these varied experiments confirm the independence of the metabolism of variations in atmospheric pressure as regards all the customary habitats of mankind. The beneficial properties of mountain air may be largely the same as those derived at watering-places, *i. e.*, outdoor life, cool air, exercise, diversion through change of scene, mental rest, and, finally, suggestion of benefits received. The dry, crisp air undoubtedly benefits catarrhal disturbances, which are, on the other hand, aggravated by the climate of the sea-shore.

In the search for conditions which might reduce the intensity of metabolism, the influence of the internal secretions of the sexual glands has been prominently considered. Careful experiments of Lüthje,[1] however, show that castration in dogs of both sexes has no influence on the metabolism. It is said, however, that removal of the ovaries reduces for a time the number of red blood-corpuscles, and it is suggested that ovarian insufficiency may be the cause of chlorosis.[2]

Grafe[3] has analyzed 29 cases of stupor, and in the majority of individuals has found no variation from the usual normal metabolism. In 8 cases, however, there was a metabolism which was between 17 and 39 per cent. lower than normal.

It has already been stated that Means, using the new Du Bois formula for surface area, could find no departure from the normal metabolism in simple obesity.

Means[4] finds a diminished metabolism in hypopituitarism with accompanying obesity. This condition of *dystrophia adiposogenitalis* is stated by Cushing[5] to show an abnormally

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[1] Lüthje: "Archiv für exp. Path. und Pharm.," 1902, xlviii, 184.

[2] Breuer and v. Seiller: *Ibid.*, 1903, l, 169.

[3] Grafe: "Deutsches Archiv für klin. Med.," 1911, cii, 15.

[4] Means: "Journal of Medical Research," 1915, xxxii, 121.

[5] Cushing: "The Pituitary Body and Its Disorders," 1912.

high tolerance for carbohydrate, whereas in acromegaly the tolerance is decreased. In acromegaly the basal metabolism is increased.[1]

Forschbach and Severin[2] (Minkowski's clinic) do not agree with Cushing, and conclude that in the most varied affections of the hypophysis (acromegaly, dystrophia adiposogenitalis, hypophyseal tumors) there is always hypoglycemia and increased carbohydrate tolerance.[3] This is illustrative of the disagreement among the best authorities upon the influence of the internal secretions.

Cushing and Goetsch[4] and, before them, Gemelli,[5] have noticed that in hibernating animals the pituitary gland not only diminishes in size, but that the cells of the pars anterior completely lose their characteristic staining reactions.

The literature regarding the action of the internal secretions upon metabolism is very large. Much of it is crudely unscientific. Where several unknown factors are interacting, as happens in this field of study, it is pleasant to give the fancy full play, and this is also a perfectly harmless occupation provided such mental activity does not develop into hallucination. Du Bois, in writing concerning exophthalmic goiter, makes the ironical proposal, "For the purpose of simplicity in this paper one may consider the symptoms of exophthalmic goiter to be caused by hypersecretion of the thyroid, and allow the reader to select for himself those cases in which he believes other glands to be involved."

The thyroid gland is a gland whose internal secretion profoundly affects the amount of general metabolism. No other gland compares with it in this regard. This influence is apparently brought about by a substance called thyroiodin,

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[1] Magnus-Levy: "Zeitschrift für klinische Medizin.," 1906, lx, 179.

[2] Forschbach and Severin: "Archiv für exp. Path. und Pharm.," 1914, lxxv, 168.

[3] For a good review of the literature read Simpson, S.: "American Medicine," 1914, ix, 219.

[4] Cushing and Goetsch: "Journal of Experimental Medicine," 1915, xxii, 25.

[5] Gemelli: "Archives pour la science medicale," 1905, xxx, 341.

which, when produced in normal quantities, maintains the proper functions of the nervous system. A subnormal production reduces the activity of the nervous system and incidentally the quantity of metabolism. An overproduction increases the irritability of the nervous apparatus and raises the metabolism. Myxedema is a condition in which the thyroid gland has atrophied and its secretion is no longer available. Exophthalmic goiter presents the opposite phase, since here a superabundance of thyroidin is believed to be produced. Symptoms somewhat akin to the latter condition may be induced in normal animals and man by ingesting thyroid extracts.

Magnus-Levy[1] found the carbon dioxid output increased after giving a normal man thyroid extracts. Fritz Voit[2] finds the same to be true of a dog, and also that more protein is metabolized. It is this latter action which contraindicates thyroid feeding in obesity. However, Rheinboldt[3] states that a man fed with thyroid extracts may be maintained in nitrogen equilibrium if much protein be allowed in the diet.

That the thyroid has a profound effect upon the endogenous protein metabolism is evidenced by the fact that after its removal in the dog the usual increases in protein metabolism which follow the administration of phlorhizin[4] (see p. 460) or which follow partial asphyxia[5] do not occur.

Andersson and Bergman[6] have given large quantities of thyroid extract to a man who was kept in perfect quiet, and no increased output of carbonic acid was noticed. They attribute the increased metabolism which is usually observed to the increased muscle tonus caused by the highly irritated central nervous system. A high metabolism is observed in cases of

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[1] Magnus-Levy: "Berliner klinische Wochenschrift," 1895, xxxii, 650.

[2] Voit, F.: "Zeitschrift für Biologie," 1897, xxxv, 116.

[3] Rheinboldt: "Zeitschrift für klin. Med.," 1906, lviii, 425.

[4] Lusk: "Proceedings of the International Congress of Medicine," 1913, Sec. II, Pt. 2, p. 13.

[5] Mansfeld: "Pflüger's Archiv," 1915, clxi, 502.

[6] Andersson and Bergman: "Skan. Archiv für Physiologie," 1898, viii, 326.

exophthalmic goiter. Freidrich Müller[1] reports a case of an individual weighing only 29 kilograms who constantly lost weight notwithstanding a daily diet containing 68 grams of protein with 58 calories per kilogram. Under such circumstances there is undoubtedly an abnormally high destruction of both protein and fat. The increased protein destruction has been attributed to toxic influence of the thyroid secretion. Magnus-Levy[2] finds an increased oxygen intake in cases of exophthalmic goiter amounting to 22, 42, and 70 per cent. above the normal.

Steyrer[3] made interesting experiments on the metabolism in this disease. The patient was twenty-one years old, temperature normal; the total metabolism during two days was determined twice at intervals one month apart and while the person was resting in bed. During the second period the disease had made considerable progress, the patient having a hot skin and being in a highly nervous state.

	Day.	Calories of Metabolism.	Weight in Kg.	Calories per Kg.
Period I	1	2665	45.1	59.1
	2	2731	46.4	58.9
Period II (one month later)	1	3666	48.2	76.1
	2	3318	47.5	69.9

Calorimetric studies upon 12 thyroid cases have been made by Du Bois[4] and the literature has been very fully considered by him. The accompanying table epitomizes the results obtained by Du Bois with 3 cases of exophthalmic goiter and with 1 cretin thirty-six years of age.

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[1] Müller: "Deutsches Archiv für klin. Medizin," 1893, li, 361.

[2] Magnus-Levy: von Noorden's "Handbuch der Pathologie des Stoffwechsels," 1907, II, p. 325.

[3] Steyrer: "Zeitschrift f. exp. Path. und Therapie," 1907, iv, 720.

[4] Du Bois: "Archives of Internal Medicine," 1916, xvii, 915.

THE METABOLISM OF 3 PATIENTS WITH EXOPHTHALMIC GOITER AND OF 1 CRETIN

Subject and Date.	Character of Experiment.	Pulse-rate.	Calories per Sq. Meter, Du Bois Formula.	Per Cent. Rise Above Normal Basal of 39.7 Cal.	Per Cent. Rise Above Patient's Own Basal.	R. Q.
Case I:						
Feb. 16, 1914.	Basal..............	137	69.4	+75	....	0.76
Feb. 20, 1914.	Basal..............	111	63.7	+60	....	0.77
Feb. 21, 1914.	Glucose, 100 gm....	105	68.8	....	+9	0.94
Feb. 25, 1914.	Casein, N = 8.9 gm.	138	71.9	....	+14	0.83
April 24, 1914.	Basal..............	120	60.9	+53	....	0.78
April 23, 1915.	Basal, one year later	99	57.7	+45	....	0.77
Case II:						
March 22, 1915.	Basal..............	107	59.4	+50	....	0.79
May 11, 1915.	Basal two weeks after ligating arteries..............	134	71.2	+79	....	0.76
Case III:						
March 12, 1915.	Basal..............	100	74.4	+87	....	0.78
Case XII (Cretin):						
April 10, 1914.	Basal..............	84	33.0	−17	....	0.92
April 14, 1914.	Glucose, 100 gm.....	88	37.9	....	+15	1.00
April 21, 1914.	Casein, N = 3.6 gm.	82	34.9	....	+13	0.93
April 23, 1914.	Basal..............	78	31.0	−22	....	0.87
May 1, 1914.	After thyroid extract	95	39.8	+0	+28	0.79

The total difference between direct and indirect calorimetry in the 12 cases was 2.9 per cent.

The specific dynamic action of protein and glucose was within the normal limits, and glucose was oxidized in an entirely normal fashion, even in the presence of some glycosuria. In one experiment (Case I) 89 per cent. of his energy production was derived from glucose.

Forschbach and Severin,[1] in Minkowski's clinic, state that the administration of 100 grams of glucose in exophthalmic goiter does not invariably produce glycosuria. The glycosuria is probably to be explained by a difficulty of glycogen retention in hyperthyroidism. When thyroid extracts are given to rabbits or to dogs the liver contains much less glycogen than normally.[2]

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[1] Forschbach and Severin: "Archiv für exp. Path. und Pharm.," 1914, lxxv, 168.

[2] Parhon: "Journal de Physiologie et de Pathologie générale," 1913, xv, 75; Cramer and Krause: "Proceedings of the Royal Society," 1913, Series B, lxxxvi, 550.

This inability to store the normal amount of glycogen is the probable explanation of the fact that the respiratory quotients found during the determinations of the basal metabolisms of patients with hyperthyroidism invariably show a lower average level than the normal.

Du Bois finds that the height of the metabolism gives the best index of the severity of the disease and classifies very severe cases as showing an increase of 75 per cent. above the normal heat production, severe cases as showing over 50 per cent., and moderately severe and mild cases as showing less than 50 per cent. increase above the normal basal metabolism. Rest of a week in bed usually caused a 10 per cent. fall in metabolism. Thyroid sera, ergotin, and quinin hydrobromate had little effect. Ligation of the thyroid arteries was followed by a rise in metabolism in most cases. There was no indication that any conservative form of treatment was more effective than mental and physical rest.

In myxedema the metabolism is reduced and there is a fall in body temperature. Anderson[1] reports a case of a woman whose metabolism was as low as 1260 calories or 18.8 per kilogram: after treatment for nine months with thyroid extracts the heat production rose to 2099 calories, or 32.3 per kilogram. These latter are normal values. The temperature rose to normal with the increase in metabolism.

The cretin investigated by Du Bois (see table on p. 442) had a basal metabolism which was 20 per cent. less than the normal adult. Response to the specific dynamic action of food was normal. The individual, by Binet's tests, had the mentality of a child of seven years, though his age was thirty-six. This condition is a rare example in which the metabolic processes are permanently depressed.

With the possession of such a gland as the thyroid, whose suppression may diminish metabolism 20 per cent. and whose stimulation may increase it 100 per cent., it is truly strange

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[1] Anderson: "Hygeia," Stockholm, 1898 (quoted in Tigerstedt's "Lehrbuch der Physiologie").

that a normal person should have a basal metabolism so regulated as to correspond to a definite heat loss per square meter of body surface. It is no wonder that the law of surface area should be assailed as incredible and irrational. The real wonder is that the law is true.

Of late years there has been a sharp differentiation between the functions of the thyroid and those of the parathyroid glands. Clonic convulsions are a symptom following parathyroidectomy, and during these periods the temperature rises. MacCallum[1] reports that the temperature of a dog, in which after parathyroidectomy violent tetany developed, rose from 39° to 43.2° during the attack. The administration of calcium acetate stopped the convulsions in a few minutes and within half an hour the temperature fell to 38.9°.

Wilson, Stearns, and Thurlow[2] report that after parathyroidectomy a condition of alkalosis develops in the blood which is neutralized by the production of acids incident to tetany, or the tetany may be prevented by intravenous injection of $\frac{M}{7}$ hydrochloric acid. The action of calcium salts is to lower the dissociation constant of hemoglobin and the alveolar tension of carbon dioxid, effects which are also brought about by acids. Underhill[3] states that neither thyroidectomy nor the simultaneous removal of two parathyroids out of four will alter the utilization of glucose by dogs. Only after the removal of three parathyroids is the assimilation limit for glucose reduced.

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[1] MacCallum: "Fever," Harvey Society Lecture, "Archives of Internal Medicine," 1908, ii, 572.

[2] Wilson, Stearns, and Thurlow: "Journal of Biological Chemistry," 1915, xxiii, 89.

[3] Underhill and Hilditch: "American Journal of Physiology," 1909–10, xxv, 66; Underhill and Blatherwick: "Journal of Biological Chemistry," 1914, xviii, 87.

CHAPTER XVI

METABOLISM IN DIABETES AND IN PHOSPHORUS-POISONING

It is said that the sweet taste of diabetic urine was familiar to Susruta, a physician who lived in India during the seventh century. The disease, then as now, may have been more prevalent among the Hindoos than elsewhere in the world. In Europe the sweet taste of diabetic urine was discovered by Thomas Willis in 1674, but it was not till after another hundred years that Dobson, in 1715, showed that the taste was due to the presence of sugar. Subsequently the coexistence of a hyperglycemia was established.

Claude Bernard found that the stimulation by puncture of a group of cells (the "diabetic center") lying in the medulla near the floor of the fourth ventricle gave rise to an excretion of sugar in the urine. This experiment is the source of the false impression that diabetes is essentially of nervous origin. It is called *la piqûre*.

Diabetes[1] is a disease of particular interest, since it is a departure from the physiologic condition involving the capacity of the organism to care for sugar in the normal fashion. All the symptoms are due to this one fact. No other disease has been more thoroughly investigated. The study of diabetes has wonderfully developed a knowledge of the intermediary metabolism of protein, fat, and carbohydrates. In presenting the details to the reader it may be remarked that the work done is prophetic of possible accomplishment along scientific lines in the study of disease. It is typical of that "scientific medicine" which affrights the spirits devoted to a passing empiricism.

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[1] For an excellent monograph on this subject consult Foster, "Diabetes Mellitus," 1915.

The foundation of modern knowledge on this subject was laid by von Mering and Minkowski[1] and by Minkowski[2] working alone, who extirpated the pancreas in dogs and demonstrated that such animals became diabetic.

Péligot[3] long ago showed that the sugar in diabetic urine was glucose. Geelmuyden[4] analyzed more than 30 diabetic urines which contained much sugar and could not detect the presence of maltose or any of the known disaccharids, though he suspected the presence of monosaccharids other than glucose. Von Noorden[5] states that fructose appears in the urine in cases of severe diabetes.

The causes of the appearance of sugar in the urine are: (1) Either the organism cannot burn sugar, which therefore accumulates in the blood in excess of the normal, and is filtered through the kidney (diabetes mellitus, experimental pancreas diabetes); or (2) some tissues may lose their sugar-retaining function so that the normal regulatory control of the quantity of blood-sugar is lost or diminished (Bernard's piqûre, alimentary glycosuria, phlorhizin glycosuria).

The stimulation of Bernard's "diabetic center" is effective in its results only when the liver contains glycogen.[6] This form of glycosuria cannot be obtained in a starving animal. It is attributed to a sudden flushing of the liver with blood and a conversion of glycogen into sugar, so that hyperglycemia and sugar elimination through the kidney follow.

Ishimori,[7] working under Hofmeister's direction, concluded that although in the fasting rabbit glycogen disappeared in the liver from the periphery of the lobule toward the center without evidence of glycogen as such appearing to be discharged, in the case of piqûre, glycogen itself passed from all

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[1] von Mering and Minkowski: "Archiv für exp. Path. und Pharm.," 1890, xxvi, 371.

[2] Minkowski: *Ibid.*, 1893, xxxi, 85.

[3] Péligot: "Compt. rend. de l'Acad. des Sciences," 1838, vii, 106.

[4] Geelmuyden: "Zeitschrift für klinische Medizin," 1910, lxx, 287.

[5] von Noorden: "Diabetes," 1905, p. 50.

[6] Dock: "Pflüger's Archiv," 1872, v, 571.

[7] Ishimori: "Biochemische Zeitschrift," 1912–13, xlviii, 332.

the cells into the surrounding lymph-spaces and dilated blood-vessels. It has been suggested that piqûre acts through a stimulation of the adrenal secretion, but Freund and Marchand[1] find after the extirpation of the adrenals that piqûre causes hyperglycemia, and argue that the adrenals are not the cause.

Hofmeister[2] has discovered that the fasting organism is more susceptible to alimentary glycosuria than the well-fed one. He calls such a condition "starvation diabetes" (see below).

Asphyxial glycosuria, discovered by Araki, has already been described (see p. 422). Macleod[3] found that if the liver were excluded from the circulation by means of an Eck fistula in the dog no hyperglycemia followed asphyxiation. Furthermore, severance of the hepatic nerves did not prevent asphyxial hyperglycemia. Macleod therefore concluded that acids carried in asphyxial blood produced glycogenolysis in the liver cells. Analogous results were obtained by Blum,[4] who found that strychnin convulsions freed a dog's liver of its glycogen even after cutting the vagus and splanchnic nerves. He concluded that chemical co-ordination was established through the blood between the muscle cells in need of sugar and the liver which could supply it.

Elias[5] found that the intravenous injection of acids into dogs resulted in a discharge of glycogen by the liver in hyperglycemia and in glycosuria. He suggested that the acidosis in diabetes mellitus might exert a similar influence. In a later paper Elias and Kolb[6] state that the hunger diabetes of Hofmeister is due to the reduced alkalinity of the blood which accompanies fasting. Administration of alkali reduced or prevented this form of glycosuria. Hence, acidosis prevents the normal storage of glycogen.

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[1] Freund and Marchand: "Archiv für exp. Path. und Pharm.," 1914, lxxvi, 324.

[2] Hofmeister: *Ibid.*, 1890, xxvi, 355.

[3] Macleod: "American Journal of Physiology," 1908–09, xxiii, 278.

[4] Blum, P.: "Pflüger's Archiv," 1915, clxi, 516.

[5] Elias: "Biochemische Zeitschrift," 1912–13, xlviii, 120.

[6] Elias and Kolb: *Ibid.*, 1913, lii, 331.

The acidosis which rapidly develops in both pancreas and phlorhizin glycosuria is, therefore, the cause of the almost complete removal of glycogen from the liver.

Minkowski[1] noted that the livers of his depancreatized dogs were free from glycogen, and this fact has been confirmed by other observers. He also found that when fructose was given glycogen could be stored.

Verzár[2] has reported that the dog does not completely lose its power to oxidize glucose until the fourth day after pancreatectomy. Intravenous injection of a 10 per cent. glucose solution sufficient in quantity to raise the blood-sugar from 0.3 to 0.9 per cent. did not thereafter affect the respiratory quotient. During the first seven days, however, injection of fructose was able to raise the respiratory quotient, though on the twelfth and twenty-first days the administration of fructose was also without effect on this quotient. One may interpret the work as indicating that on the fourth day the organism lost the power to split glucose, whereas the ability to break fructose into oxidizable trioses or methyl-glyoxal remained intact. Later, the power to oxidize the three carbon atom chains was also lost, though the power to produce them and reconstruct them into glucose was preserved. There is no evidence existing which proves that sugar in order to be oxidized must first be converted into glycogen. That the diabetic liver cannot form glycogen from glucose appears from the experiments of Epstein and Baehr,[3] who performed pancreatectomy and double nephrectomy upon a cat which had fasted nine days. The blood-sugar, which before the operation had been 0.06 per cent., rose to 1.1 per cent. forty-eight hours after the operation, at which time the animal was killed. The liver proved to be free of glycogen and the muscle contained only 0.06 per cent. of the substance.

Glycosuria which follows exposure to cold, as originally

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[1] Minkowski: *Loc. cit.*

[2] Verzár: "Biochemische Zeitschrift," 1914, lxvi, 75.

[3] Epstein and Baehr: "Journal of Biological Chemistry," 1916, xxiv, 1.

observed by Araki,[1] is very likely due to the asphyxial element brought about by vasoconstriction.

Böhm and Hoffmann[2] report that a dog barking at a cat induces glycosuria in the cat. Cannon and de la Paz[3] term this "emotional glycosuria," and have found that the cat's blood contains an increased quantity of epinephrin as a sequence to the fright. This increased amount of epinephrin becomes the exciting cause of dilatation of the pupil, inhibition of the movements of stomach and intestines, acceleration of the heart, erection of the hairs on the back and on the tail, and the discharge of glycogen.

Cannon has elaborated these results and presented them in the form of a popular book which holds that emotional impulses act upon the adrenals, causing them to discharge epinephrin, which, in turn, mobilizes the physical and chemical resources of the body for supreme mechanical effort in both attack and defense.

Tying down a frightened rabbit to a board results in psychic glycosuria, the blood-sugar rising to 0.4 or 0.5 per cent. and the urine containing as high as 7.8 per cent. of sugar.[4]

The urines of 34 men and of 36 women students were tested by Folin[5] before and after college examinations: 6 men and 6 women showed small but unmistakable traces of glycosuria immediately after examination. This further illustrates the phenomenon of emotional glycosuria.

Alimentary glycosuria is seen in normal animals and in man when sugar is given in larger quantities than the glycogen regulatory function can care for. Moritz[6] found 2 grams of

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[1] Araki: "Zeitschrift für physiologische Chemie," 1892, xvi, 454; see also Wacker: *Ibid.*, 1910, lxvii, 197.

[2] Böhm and Hoffmann: "Archiv für exp. Path. und Pharm.," 1878, viii, 280.

[3] Cannon, Shohl, and Wright: "American Journal of Physiology," 1911, xxix, 280.

[4] Hirsch and Reinbach: "Zeitschrift für physiologische Chemie," 1913, lxxxvii, 122.

[5] Folin, Denis, and Smillie: "Journal of Biological Chemistry," 1914, xvii, 519.

[6] Moritz: "Verhandlungen des 10ten Congresses für innere Medizin," 1891, p. 492.

glucose in the urine of a man after the ingestion of 200 grams. Such an alimentary glycosuria lasts between three and six hours.

Moritz[1] observed 0.2 to 0.3 per cent. of sugar in the urine of 4 out of 6 healthy people who had partaken of a quantity of sweets and champagne.

Evidently such conditions as these are not to be classed with diabetes mellitus, where there is a fundamental disturbance in the sugar-burning power in the organism. It would be of service to distinguish between glycosurias where the *sugar-holding* capacity of the organs has been diminished or overstrained, and the glycosuria of *diabetes* in which the *sugar-burning* capacity has been affected. For example, Kleiner and Meltzer[2] injected intravenously 4 grams of glucose per kilogram of animal into both normal and depancreatized dogs. The blood-sugar rose greatly in both groups of animals, but in the normal animals there was a rapid readjustment through elimination by the kidney, glycogen retention, and oxidation of glucose, whereas in the depancreatized animals, though removal of the glucose by the kidney was active, the other two functions were in abeyance and the blood-sugar continued at a high level long after it had readjusted itself in the normal animals.

A special type of glycosuria is caused by phlorhizin[3] injections, as was discovered by von Mering.[4] Here the blood itself while passing through the kidney loses the power of retaining its normal sugar content and a hypoglycemia results. Sometimes when the kidney is altered in Bright's disease phlorhizin is ineffective and no glycosuria follows its administration. The renal character of phlorhizin glycosuria was demonstrated by Zuntz,[5] who placed cannulæ in the upper portions of the two

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[1] Moritz: "Deutsches Archiv für klinische Medizin," 1890, xlvi, 217.

[2] Kleiner and Meltzer: "American Journal of Physiology," 1914–15, xxxvi, 361.

[3] Lusk: "Phlorhizinglukosurie, Ergebnisse der Physiologie," 1912, xii, 372.

[4] von Mering: "Verhandlungen des 5ten Congresses für innere Medizin," 1886, p. 185.

[5] Zuntz: "Archiv für Physiologie," 1895, p. 570.

kidneys and injected phlorhizin into the renal artery of one. On the injected side sugar-containing urine appeared in two minutes, and three minutes later the kidney on the opposite side yielded sugar through its ureter. The delay was due to the lapse of time necessary for the transportation of the phlorhizin by the blood-stream from the injected kidney to the other one. In this form of glycosuria sugar ingested *per os*, or subcutaneously, or as formed in protein metabolism, is all eliminated in the urine.[1]

Extirpation of the spleen has no influence upon the course of phlorhizin glycosuria.[2] Nor has the establishment of an Eck fistula.[3] An Eck fistula is one which diverts the whole of the portal circulation to the liver into the inferior vena cava, and leaves the liver supplied by the hepatic artery only. In this case the ingestion of glycocoll by the animal resulted in its complete transformation into urinary glucose, showing that the diversion of blood away from the liver in no way affected the synthetic production of sugar from this amino-acid.

Levene found that the bile contained a small amount of glucose after the administration of phlorhizin, and this has been confirmed by Woodyatt.[4]

Loewi[5] has conceived the idea that the blood-sugar is normally in a loose combination with colloid substance. This colloid sugar cannot pass through the glomerulus. If, however, sugar accumulates in the blood above the combining power of the colloid, then the crystalloid glucose readily passes away through the kidney. This condition exists in diabetes mellitus. In phlorhizin glycosuria the kidneys break up the colloid sugar, and the sugar may then be eliminated. Stiles and Lusk, while accepting Loewi's theory, have added the hypothesis that the colloid sugar cannot be burned. Phlorhi-

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[1] Stiles and Lusk: "American Journal of Physiology," 1903, x, 67.
[2] Austin and Ringer: "Journal of Biological Chemistry," 1913, xiv, 139.
[3] Sweet and Ringer: *Ibid.*, p. 135.
[4] Woodyatt: *Ibid.*, 1909–10, vii, 133.
[5] Loewi: "Archiv für exp. Path. und Pharm.," 1902, xlviii, 410.

zin acting in the kidney will split the compound and permit the elimination of sugar. Any free glucose in the general circulation unites with the colloid radical and is protected from combustion, as is the case when 5 grams of glucose are administered subcutaneously, only to reappear in the urine (Stiles and Lusk). The presence of a colloid-glucose combination is denied by Rosenfeld and Asher,[1] who find that the sugar of normal blood is readily diffusible.

It was discovered by Ringer[2] that when a large quantity of glucose (75 grams) is given to a phlorhizinized dog it is completely eliminated in the urine, and Lusk found that the ingestion of this large quantity in no way affects the respiratory quotient (see p. 244). It is therefore evident that the completely phlorhizinized dog has lost the power of oxidizing glucose. This probably does not occur on the first day of the administration of phlorhizin and may possibly be due to the development of acidosis (see p. 261). Stanley Benedict[3] reports that administration of glucose to the phlorhizinized dog causes the amount of blood-sugar to rise above the normal, which shows that sugar is present in ample concentration though it remains chemically untouched.

Phlorhizin glycosuria is only temporary in character, and subcutaneous injections of alkaline solutions of the drug three or four times daily have been employed in order to obtain constant results.

A more convenient method is that of Coolen,[4] who noticed that the subcutaneous injection of 1 gram of phlorhizin suspended in 7 c.c. of olive oil caused a glycosuria of maximal intensity which lasted between five and ten days. Common laboratory practice at present calls for daily injections of this material.

The character of phlorhizin glycosuria has been dwelt upon

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[1] Rosenfeld and Asher: "Zentralblatt für Physiologie," 1905, xix, 449.

[2] Ringer: "Journal of Biological Chemistry," 1912, xii, 431.

[3] Guion, C. M., and Benedict, S. R.: Paper read before the American Society of Biological Chemists, 1915.

[4] Coolen: "Archives de Pharmacodynamie," 1895, i, 267.

because the protein metabolism is here identical with that observed in diabetes mellitus.

Von Mering and Minkowski[1] removed the pancreas from dogs and obtained a condition which was markedly analogous to diabetes mellitus in man. There is hyperglycemia and a large excretion of glucose in the urine; ingested glucose cannot be burned, but is completely eliminated. The dogs show a considerable acidosis with excretion of β-oxybutyric acid, and they die in coma.[2] If a portion of the gland remain in the abdominal cavity there is either no diabetes or only a partial diabetes. Minkowski[3] reports that if a piece of the pancreas be ingrafted under the skin of a dog and afterward the whole of the remainder of the pancreas be removed from the abdomen, the dog's urine remains free from sugar for two months, but on extirpation of the piece ingrafted under the skin an extreme diabetes sets in.

Allen[4] reports that a dog which has a large part of its pancreas removed, but is free from diabetes, may gradually become diabetic by giving protein and fat, and may then manifest the spontaneous downward progress observed in human patients.

By an operation which united the blood supply of two dogs Forschbach[5] established the condition of parabiosis. On the removal of the pancreas from one of the dogs neither developed diabetes. An analogous experiment is that of Carlson,[6] who performed pancreatectomy upon bitches near to term and found little or no sugar in the urine. Here the embryo apparently furnished the mother with the substance essential to sugar oxidation. Murlin, however, in unpublished experiments finds that such dogs have diabetic respiratory quotients

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[1] von Mering and Minkowski: "Archiv für exp. Path. und Pharm.," 1890, xxvi, 371.

[2] Allard: *Ibid.*, 1908, lix, 391.

[3] Minkowski: *Ibid.*, 1908, Supplement-band, p. 399.

[4] Allen, F. M.: "Harvey Lectures," 1916–17.

[5] Forschbach: "Archiv für exp. Path. und Pharm.," 1909, lx, 131.

[6] Carlson, Orr, and Jones, W. S.: "Journal of Biological Chemistry," 1914, xvii, 19.

(0.69), and suggests that the absence of glucose from the urine is due to carbohydrate retention by the fetus.

It has long been known that diabetics eliminate sugar even after all administration of sugar is stopped. It has also been generally recognized that protein ingestion tends to increase the sugar output in the urine, while fat has no effect.

A large amount of information has been collected concerning the relation between the urinary nitrogen and sugar elimination in the fasting and meat-fed diabetic organism. The dextrose to nitrogen ratio (D : N) is a key to the problem of the quantity of sugar which can be derived from protein metabolism (p. 173).

Minkowski[1] was the pioneer who discovered that depancreatized dogs, whether fasting or fed with meat, showed a constant elimination of 2.8 grams of glucose for each gram of nitrogen in the urine. This ratio (D : N : : 2.8 : 1) was the average obtained from 7 dogs on twenty-two different days. The lowest ratio was 2.62 : 1, the highest 3.05 : 1. Some other operators have been unable to obtain these ratios. Pflüger[2] finds a variable and generally lower ratio, and his dogs all died of abscesses. Embden's[3] ratios are all lower than Minkowski's, and are probably due to incomplete extirpation of the pancreas.

The accuracy of Minkowski's results is indicated by the fact that the ratio (D : N : : 2.8 : 1) may be easily established by the administration of phlorhizin to rabbits, goats, cats, and in certain dogs whose kidneys have been somewhat affected, as, for example, by giving camphor. Phlorhizin acts first to cause a sweeping out of the excess of sugar in the organism, with a subsequent establishment of the ratio. (See table, p. 463.) The ratios in different animals are given in the following table:

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[1] Minkowski: "Archiv für exp. Path. und Pharm.," 1893, xxxi, pp. 85, 97.

[2] Pflüger: "Das Glycogen," 1905, p. 491.

[3] Embden and Salomon: "Hofmeister's Beiträge," 1905, vi, 63.

RATIOS IN DIABETES OF D : N : : 2.8 : 1

Day.	Dog.[1]	Dog.[2]	Cat.[3]	Goat.[4]	Rabbit.[5]
	Pancreas Diabetes.	Phlorhizin and Camphor.	Phlorhizin.	Phlorhizin.	Phlorhizin.
Second day of diabetes.	. .	. .	. .	2.95	2.89
Third day of diabetes. .	2.88	. .	2.93	2.90	2.69
Fourth day of diabetes.	2.94	. .	2.80	2.78	
Fifth day of diabetes. .	3.09	. .	2.93		
Day unknown.	. .	2.8			

The uniformity of the ratio as shown in different animals is very striking. One may calculate from these results that 45 per cent. of the protein molecule may be converted into dextrose in the course of metabolism.

This, however, does not complete the story of the D : N ratio, for a higher ratio, or 3.75 : 1, was discovered by Reilly, Nolan, and Lusk[6] in the urine of dogs with normal kidneys, after subcutaneous injections of phlorhizin. This ratio was subsequently revised by Stiles and Lusk[7] and found to be 3.65 : 1. The importance of this discovery was enhanced by the finding of Mandel and Lusk[8] that the same ratio may exist in human diabetes when the patient is given a diet of meat and fat. The ratios found on successive days are thus comparable:

Phlorhizinized Dog.	Phlorhizinized Man.	Diabetes Mellitus in Man.	
3.60[9]	3.58[10]	3.60[11]	3.75[12]
3.65	3.82	3.65	3.56
3.66	3.66	3.66	3.70
3.62			
3.63	3.68	3.64	3.66

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[1] Minkowski: *Loc. cit.*, p. 97.

[2] Jackson: "American Journal of Physiology," 1902, viii, p. xxxii.

[3] Arteaga: *Ibid.*, 1901, vi, 175.

[4] Lusk: "Zeitschrift für Biologie," 1901, xlii, 43.

[5] Reilly, Nolan, and Lusk: "American Journal of Physiology," 1898, i, 396.

[6] Reilly, Nolan, and Lusk: *Loc. cit.*

[7] Stiles and Lusk: "American Journal of Physiology," 1903, x, 67.

[8] Mandel and Lusk: "Deutsches Archiv für klin. Medizin," 1904, lxxxi, 479.

[9] Stiles and Lusk: *Loc. cit.*, p. 77. (Details, this book, p. 99.)

[10] Benedict, S. R., and Lewis, R. C.: "Proceedings of the Society for Experimental Biology and Medicine," 1914, xi, 134. (Details unpublished.)

[11] Mandel and Lusk: *Loc. cit.*, p. 479.

[12] Greenwald: "Journal of Biological Chemistry," 1913–14, xvi, 375.

In another place (p. 174) it has been shown that the D : N ratio does not vary after the ingestion of sufficient meat to double the quantity of nitrogen in the urine; the sugar also doubles. The sugar production is therefore proportional to the protein metabolism, and, apparently, must be derived from protein.

Various objections have been raised to this statement. Other experiments, however, confirm the above proposition.

Lüthje[1] gave "nutrose" to a depancreatized dog. "Nutrose" contains casein, but no sugar. The dog weighed 5.8 kilograms and eliminated 1176 grams of glucose during twenty-five days. The tissues of the dog could not possibly have contained over 232 grams of glycogen at the beginning of the experiment. The source of the sugar could not have been the animal's store of glycogen, but it must have arisen from either protein or fat.

The D : N ratio of 3.65 : 1 was accepted by Lusk as being true for the dog because the greater number of the higher ratios which were found were established at this level. Janney[2] prefers to take the average of all determined D : N ratios and in this way arrives at a ratio of 3.43 : 1. He argues that, since 4.7 per cent. of the urinary nitrogen is in the form of creatin and creatinin, which are not glucose formers, a correction would bring up the D : N ratio in the dog to 3.60. Although it is not clear why the urinary creatin and creatinin should be thus subtracted, for they are as truly metabolism products of protein as is urea, still Janney's[3] experiments, which show the quantities of glucose produced from various forms of flesh, as determined through feeding experiments with the phlorhizinized dog, are of great interest and may thus be presented:

SPECIES OF FLESH.	MAN.	DOG.	RABBIT.	OX.	CHICKEN.
D : N ratio	3.6	3.6	3.8	3.6	3.4
Glucose per 100 gm. of protein metabolized	58	58	60	58	54

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[1] Lüthje: "Pflüger's Archiv," 1905, cvi, 160.
[2] Janney and Csonka: "Journal of Biological Chemistry," 1915, xxii, 203.
[3] Janney and Blatherwick: *Ibid.*, 1915, xxiii, 77.

According to Janney,[1] the percentage quantity of glucose derivable from the following proteins is: casein 48, ovalbumin 54, serum albumin 55, gelatin 65, fibrin 53, edestin 65, gliadin 80, and zein 53 per cent.

Pflüger[2] would have it that fat metabolism is the principal source of sugar in diabetes.

Giving fat with meat to a diabetic will not ordinarily increase the sugar in the urine. The writer has never observed such an increase in any of the work of his laboratory. A large production of sugar from fat has been elsewhere reported,[3] and Cremer[4] finds that glycerin alone will increase the output of sugar in the urine. (See p. 262.)

On giving meat in diabetes the fat metabolism is reduced as it would be in the normal organism, and yet there is no effect on the D : N ratio, and therefore the latter cannot be influenced by the *quantity* of fat burned. This is shown in a respiration experiment made by Mandel and Lusk[5] on a dog with phlorhizin glycosuria whose metabolism starving and after meat ingestion was as follows:

	D : N.	Calories from Protein.	Calories from Fat.	Calories, Total.
Fasting	3.69	80.2	274.4	354.6
300 grams meat	3.55	161.9	261.7	423.6

The protein metabolism doubled when meat was ingested, the fat metabolism fell, but the D : N ratio remained constant.

It has also been demonstrated that neither exposure to cold nor mechanical exercise, both of which result in a largely increased metabolism of fat, has any effect on the sugar output in pancreas diabetes[6] or in phlorhizin glycosuria.[7] Freund and Marchand[8] found that ten hours' exposure to the winter's

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[1] Janney: "Journal of Biological Chemistry," 1915, xx, 321.

[2] Pflüger: "Pflüger's Archiv," 1905, cviii, 115.

[3] Hartogh and Schumm: "Archiv für exp. Path. und Pharm.," 1901, xlv, 11.

[4] Cremer: "Münchener med. Wochenschrift," 1902, xlix, 944.

[5] Mandel and Lusk: "American Journal of Physiology," 1903, x, 54.

[6] Allard: "Archiv für exp. Path. und Pharm.," 1908, lix, 111; Seo, *Ibid.*, p. 341.

[7] Lusk: "American Journal of Physiology," 1908, xxii, 163.

[8] Freund and Marchand: "Archiv für exp. Path. und Pharm.," 1913, lxxiii, 276.

cold reduced the blood-sugar of a phlorhizinized dog to zero. The writer found in a phlorhizinized dog which had been rid of glycogen by shivering and exercise that the composition of the urine was unchanged as the result of traveling 1500 meters in a revolving wheel, an effort which would have more than doubled the metabolism of fat during the hour when the exercise was taken. The analytic data for two-hour periods were the following:

	Glucose.	Nitrogen.	D : N.
Rest	4.57	1.26	3.63
Work, 1500 meters during first hour	4.62	1.26	3.67

In this experiment exercise was without influence on the excretion of nitrogen. If, however, the animal contains residues of glycogen which as a result of exercise are converted into sugar and eliminated, then there is also an increased nitrogen elimination as the result of work. This is suggestive of a chemical union between glycogen and nitrogenous substances.

The theory of the origin of sugar from fat was supported by Falta,[1] who found a largely increased sugar output after administering adrenalin to dogs with pancreas diabetes. Among the cases of high D : N in human diabetes reported from von Noorden's clinic that described by Bernstein, Bolaffio, and Westenrijk[2] is the most remarkable. The ratio, after deducting the carbohydrates ingested in the food, often reached D : N : : 10 : 1. The high ratios in diabetes are explained by Falta as being due to very great activity on the part of the adrenals which not only inhibits the internal secretion of the pancreas, but also causes a production of sugar from fat. However, Ringer,[3] working in the author's laboratory, finds that if adrenalin be administered to a fasting phlorhizinized dog, although the first administration of the drug may bring about an elimination of "extra sugar" which

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[1] Eppinger, Falta, and Rudinger: "Zeitschrift für klinische Medizin," 1908, lxvi, 1.

[2] Bernstein, Bolaffio, and Westenrijk: *Ibid.*, 1908, lxvi, 378.

[3] Ringer: "Journal of Experimental Medicine," 1910, xii, 105.

may be discharged from the glycogen repositories of the body on account of the anemia of the tissues (see p. 447), a second injection of adrenalin may be entirely without influence on either the sugar or nitrogen elimination. This indicates that adrenalin does not cause a production of sugar from fat.

The high D : N ratios reported above, as well as many similar observations described in the literature, are unquestionably due to the surreptitious ingestion of food containing carbohydrate.

Falta explains the results of many experiments by stating that while the secretory activities of thyroid and adrenals are each stimulated by the secretions of the other, the activity of the pancreas is in like manner inhibited by the secretions of the other two glands. Therefore supersecretion of adrenalin inhibits the secretory function of the pancreas so that the organism can no longer oxidize carbohydrates, and at the same time it stimulates the thyroid, causing increased protein metabolism. Furthermore, in exophthalmic goiter, where there is supersecretion in the thyroid gland, there is a tendency to glycosuria, and it is believed that true diabetes has been induced by this cause.[1] Administration of thyroid extracts to dogs also produces glycosuria. Cecil,[2] working under Opie's direction, finds lesions of the pancreas in cases of diabetes associated with exophthalmic goiter, and Forschbach and Severin,[3] in Minkowski's clinic, believe that there is very likely a slight disturbance of the pancreas in some cases of hyperthyroidism.

The complicated theorizing of the von Noorden school, as represented by Falta's statements, found early acceptance among clinicians. However, there are many demonstrable errors in the presentation. Thus Ringer, in the experiments mentioned above, found no increase in the protein metabolism

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[1] Magnus-Levy: von Noorden's "Handbuch des Stoffwechsels," 1907, Bd. ii, p. 333.

[2] Cecil: "Journal of Experimental Medicine," 1909, xi, 266.

[3] Forschbach and Severin: "Archiv für exp. Path. und Pharm.," 1914, lxxv, 168.

of his dogs after giving them epinephrin, and Lusk[1] found the same to be true in normal dogs, and also discovered that if glucose were given to normal dogs and then epinephrin were administered the respiratory quotient rose to unity, showing a normal combustion of carbohydrate.

Fuchs and Róth[2] state that the respiratory quotient increases in human beings after the subcutaneous injection of epinephrin, as appears below:

Before.	Epinephrin.	After.
0.85	*0.91*	0.84
0.87	*0.96*	0.86

It is evident that the theory that epinephrin causes a production of sugar from fat, decreases the power of the organism to oxidize glucose through inhibition of pancreatic function, and stimulates the thyroid so that protein metabolism is increased, is untenable in any of its particulars.

In the matter of the thyroid being the cause of the high protein metabolism in diabetes, von Noorden is right. Eppinger, Falta, and Rudinger[3] extirpated both pancreas and thyroid and found that the protein metabolism was almost the same as in the normal dog instead of being increased three- or fourfold, as occurs when the pancreas alone is extirpated. The D : N ratio was at first 3.5, but declined after a few days to 2.8.

Von Noorden suggested to the writer of this book that the increased total metabolism which follows the administration of phlorhizin (see p. 474) would not take place if the thyroid gland had been previously extirpated. Lusk[4] determined the metabolism of a dog after complete thyroidectomy with removal of three parathyroids and found it to be 19 calories per hour, whereas after phlorhizin administration values of 20.3

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[1] Lusk: "Archives of Internal Medicine," 1914, xiii, 673.

[2] Fuchs and Róth: "Zeitschrift für ex. Path. und Ther.," 1912, x, 187.

[3] Eppinger, Falta, and Rudinger: "Zeitschrift für klinische Medizin," 1908, lxvi, 1.

[4] Lusk: Proceedings of the XVIIth International Congress of Medicine, Section on Physiology, London, 1913, p. 13.

and 19.3 calories per hour were found, determined one and three days after diabetes had been induced. The usual rise in protein metabolism and total metabolism were absent. After the ingestion of meat, however, the heat production increased and rose on one occasion from a basal value of 17.5 to 26 calories per hour, an increase of 50 per cent. The urinary nitrogen largely increased and the process of amino-acid stimulation was in full play, notwithstanding the absence of the thyroid gland. This naturally suggests the hypothesis that the reason why there is no increased heat production in diabetes after thyroidectomy is that there is no rise in the quantity of protein metabolized.

As shown by Parhon and by Cramer (see p. 442), thyroid ingestion causes the liver to discharge glycogen. Conversely, after thyroid extirpation the liver should retain glycogen more tenaciously than before. This, at least, would explain the long continued high D : N ratios observed by Lusk in phlorhizinized dogs after thyroidectomy and by Miura[1] in rabbits similarly treated.

In contradiction to the statements of Eppinger, Falta, and Rudinger, and of Miura, Underhill[2] finds that epinephrin glycosuria may be as easily produced in thyroidectomized as in normal animals.

The subject of the correlation between the various glands of internal secretion is evidently one as replete with opportunities for the play of the imagination as it is for enlightening experimental research.

A question of special interest is the cause of the two D : N ratios, 2.8 : 1 and 3.65 : 1. The former represents a production of 45 per cent., the latter one of 58 per cent. of sugar from meat protein. In neither case can ingested glucose be burned. It is, of course, possible that the sugar production varies under different circumstances; that is to say, the organism (liver?) may be able at times to produce sugar from a certain class of

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[1] Miura: "Biochemische Zeitschrift," 1913, li, 423.

[2] Underhill: "American Journal of Physiology," 1910–11, xxvii, 331.

protein decomposition products, and at other times not. For example, it has been noted (p. 201) that glutamic acid is convertible into glucose in the dog, but Neuberg[1] testifies that it may also be converted into butyric acid from which sugar cannot be formed. Or, one may adopt the hypothesis of Mandel and Lusk,[2] which assumes a difference between α-colloid glucose and β-colloid glucose existing in the blood. By α-glucose is understood the amount of glucose represented by the ratio D : N : : 2.8 : 1, or 45 per cent. of the protein. The β-glucose represents the additional 13.6 per cent. of the protein, when the ratio 3.65 : 1 is present. The ratio would depend on the combustion or non-combustion of the β-glucose. If the latter burns, it must do so as a complex, for as free glucose it would be eliminated in the urine.

This theory of a difference in chemical union would explain the fact discovered by Straub[3] for carbon monoxid "diabetes" and by Seelig[4] for glycosuria following ether inhalation, that sugar appears in the urine in large quantity if a dog be fed with meat, but disappears if the animal be given carbohydrate alone. Seelig found no glycosuria when an intravenous infusion of oxygen was administered at the same time that ether was given. It may be that lack of oxygen causes a dissociation of either α- or β-colloid glucose derived from protein, which glucose then appears in the urine. This suggestion is, however, highly speculative.

One of the very pronounced characteristics of the diabetic is his constant emaciation. There is usually a larger excretion of nitrogen in the urine than is necessary for a healthy person. It may be recalled that carbohydrates diminish the protein metabolism, and also that a person may support life on meat and fat alone without tissue waste. But in this latter case there is a supply of carbohydrate derived from protein metab-

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[1] Brasch and Neuberg: "Biochemische Zeitschrift," 1908, xiii, 299.

[2] Mandel and Lusk: "Deutsches Archiv für klinische Medizin," 1904, lxxxi, 491.

[3] Straub: "Archiv für exp. Path. und Pharm.," 1897, xxxviii, 139.

[4] Seelig: *Ibid.*, 1905, lii, 481.

olism. This is also true in starvation. But when the protein sugar is withdrawn from the tissue cells in diabetes, there is at once a largely increased protein metabolism. This is most obvious in fasting animals treated with phlorhizin, as the glycosuria can be immediately induced. The increase in protein metabolism is most marked where the higher D : N ratio exists. In this connection the following experiments on fasting animals are suggestive:

TABLE ILLUSTRATING THE INFLUENCE OF DIABETES ON PROTEIN METABOLISM

	Goat.[1]			Dog.[2]		
	D.	N.	D : N.	D.	N.	D : N.
Fasting	.....	3.72	....	.....	4.04	....
Fasting	.....	3.71	....	.....	4.17	....
Fasting and diabetic	20.33	4.90	4.15	63.55	12.66	5.02
" "	26.08	8.83	2.95	65.30	18.76	3.38
" "	23.39	8.06	2.90	65.84	18.57	3.54
" "	19.01	6.84	2.78	64.80	17.29	3.74

In the goat the protein metabolism rose to 238, in the dog to 450 per cent. of that in the normal animals, as the result of the loss of the influence of the small quantity of protein sugar produced in starvation.

Falta, Grote, and Staehelin[3] found increases in the protein metabolism of fasting dogs which had been depancreatized, equal to three- and fivefold the normal amount.

In the case of diabetes mellitus reported by Mandel and Lusk where the ratio D : N was 3.65 : 1, it was found that the ingestion of broths containing 7.7 grams of nitrogen was followed by an elimination of 21.7 grams of nitrogen in the urine or a loss of body nitrogen approximating 14 grams. The patient was greatly emaciated, and passed this day in bed.

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[1] Lusk: "Zeitschrift für Biologie," 1901, xlii, 43.

[2] Reilly, Nolan, and Lusk: "American Journal of Physiology," 1898, i, 397.

[3] Falta, Grote, and Staehelin: "Hofmeister's Beiträge," 1907, x, 199.

He could not be maintained in nitrogen equilibrium with 19 grams of protein nitrogen in the food, but was in nitrogen equilibrium when given 27 grams. In all cases of intense diabetes this factor of an increased protein metabolism must be considered. In mild cases in which sugar disappears from the urine when carbohydrates are cut out of the food, and in which the patient may burn his protein sugar, the protein metabolism is not different from that of a normal person living on meat and fat.

As would be expected under conditions involving an increase in protein metabolism, amino-acids are found in increased quantities in both blood and urine of diabetic patients.[1]

The preëminence of fat metabolism in the diabetic as the mainstay of his organism leads to inquiry as to the origin of the fatty acid called β-oxybutyric acid, and of aceto-acetic acid and aceton which are directly derived from it.[2] Whence do these aceton bodies arise? They were at first supposed to come from glucose, following a chemical process analogous to the butyric acid fermentation of carbohydrates, but it was soon discovered that in normal persons the aceton bodies were especially found in the fasting state. Many then attributed the presence of aceton to the specific breakdown of body protein, since, when protein was given in the food, the aceton bodies disappeared in the urine. However, Magnus-Levy[3] has reported a case of a boy in coma who eliminated an average of 97.5 grams of β-oxybutyric acid and aceto-acetic acid daily for three days in addition to an unmeasured quantity of aceton in the breath, and during this time the protein metabolism amounted to 90 grams, of which latter at least 40 grams appeared as sugar in the urine. The 97.5 grams of aceton bodies in this case could not have been entirely derived from

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[1] Galambos and Tausz: "Zeitschrift für klin. Med.," 1913, lxxvii, 14; 1914, lxxx, 381. Löffler: *Ibid.*, 1913, lxxviii, 483.

[2] This description is taken from Lusk: "Metabolism in Diabetes," Harvey Society Lecture, "Archives of Internal Medicine," 1909, iii, 1.

[3] Magnus-Levy: "Ergebnisse d. inn. Med.," 1908, i, 374.

the 90 grams of protein, but they must have originated largely from fat.

Stadelman[1] first pointed out the relationship between the formation of β-oxybutyric acid and the occurrence of coma. Coma has been compared to the sword of Damocles which hangs suspended over every diabetic. It has been discovered that whenever the organism is thrown suddenly from a carbohydrate regimen to a combustion of fat the aceton bodies appear in the urine. This condition is greatly intensified in diabetes when even the sugar derived from protein is not burned.

Each molecule of butyric acid can yield one of β-oxybutyric acid. It has been calculated by Magnus-Levy[2] that 100 grams of neutral fat made of stearin, palmitin, and olein may yield 36.2 grams of β-oxybutyric acid. It is therefore evident that the higher fatty acids are the more valuable nutriment. Butter, with its high content of butyric acid, largely increases the output of the aceton bodies in diabetes; 50 to 100 grams of butter fat when administered to a diabetic may raise his urinary aceton four- to eightfold.[3] Oleomargarin is to be preferred.

Magnus-Levy[4] gave 11.7 grams of β-oxybutyric acid to a normal dog. This was completely burned. He then gave 11.5 grams to a phlorhizinized dog, with the result that there was an increased elimination of 7.6 grams of β-oxybutyric acid and aceton. Since some aceton was eliminated in the breath, it is evident that the animal had largely lost the power to burn ingested β-oxybutyric acid.

The evidence concerning the formation of the aceton bodies from fat and from some amino-acids has already been discussed (see p. 208). It suffices here to recall that Otto Neubauer[5] found that the ingestion of either β-oxybutyric

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[1] Stadelman: "Experimentelle-klinische Untersuchungen," Stuttgart, 1890.

[2] Magnus-Levy: "Ergebnisse d. inn. Med.," 1908, i, 384.

[3] Fejes: "Magyar orvosi Archivum," 1907, viii, 335.

[4] Magnus-Levy: "Ergebnisse d. inn. Med.," 1908, i, 372.

[5] Neubauer, O.: "Verhandlungen des deutschen Congresses für innere Medizin," 1910, xxvii, 566.

acid or aceto-acetic acid by a diabetic patient always caused the partial excretion of the one given in the form of the other. The reaction is reversible:

$$CH_3.CHOH.CH_2.COOH + O \rightleftarrows CH_3.CO.CH_2.COOH + H_2O.$$

In marked acidosis Neubauer found that β-oxybutyric acid amounted to between 60 and 80 per cent. of the total urinary aceton bodies.

If a surviving liver be perfused with blood containing β-oxybutyric acid, the latter is in part converted into aceto-acetic acid.[1] Minced liver or even the aqueous extract of liver tissue will effect the same reaction.[2]

Fischler and Kossow[3] report that the formation of aceton bodies in a phlorhizinized dog is decreased in the presence of an Eck fistula, whereas if a "reversed" Eck fistula be created by diverting the blood from the vena cava into the portal vein, the excretion of aceton bodies is increased fivefold. This points to the liver as the main source of the aceton bodies, if one may accept conclusions drawn from experimental conditions so profoundly abnormal.

The quantity of the aceton bodies in the blood is given by Marriott[4] as follows:

	In 100 C.C. of Blood.	
	Aceto-acetic Acid and Aceton.	β-oxybutyric Acid.
	Milligrams.	Milligrams.
Normal dog	0.04	3.2
	0.08	1.7
	0.06	1.7
Normal child	0.06	4.4
	0.08	4.4
Phlorhizinized dog	7.2	10.4
Diabetic child in coma	23.4	24.8

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[1] Embden and Engel: "Hofmeister's Beiträge," 1908, xi. 323.

[2] Wakeman and Dakin: "Journal of Biological Chemistry," 1909, vi, 373.

[3] Fischler and Kossow: "Deutsches Archiv für klin. Med.," 1913, cxi, 479.

[4] Marriott: "Journal of Biological Chemistry," 1913–14, xvi, 293.

The increase in the aceton bodies in the blood is greatest in diabetes mellitus in man, is not so marked in phlorhizin glycosuria in dogs, and is least of all present in depancreatized dogs. Sassa[1] states that the organs of diabetic men dying in coma may contain eight times the normal quantity of β-oxybutyric acid, the liver showing relatively the greatest storage of the substance. In one instance (Case II) 130 milligrams of β-oxybutyric acid were found in 100 grams of the body tissue of a man weighing 70 kilograms, and the author computes the presence of 85 grams of the substance within the body. Marriott's[2] highest figures for 100 c.c. of diabetic blood in man are 28 milligrams of aceto-acetic acid and 45 milligrams of β-oxybutyric acid.

The demonstration by Ringer[3] that propionic acid was completely converted into glucose and that higher fatty acids with *uneven* numbers of carbon atoms yielded glucose in so far as they might form propionic acid by β-oxidation, presents the theoretic possibility of giving to diabetics fats containing these fatty acids, which would yield innocuous glucose instead of acid bodies as the end-products of oxidation. Practical difficulties in the preparation of such fats have alone prevented Ringer from testing the efficiency of their administration to diabetic subjects.

The result of the formation of acid bodies in the organism leads to a condition of *acidosis*, the alkali reserves being called upon. Not only does ammonia increase in the urine, but there may be a marked fall in the carbon dioxid content of the blood due to a diminution in the quantity of bicarbonate of soda. Magnus-Levy[4] reports an extreme case in which 100 c.c. of the blood of a diabetic just before death in coma contained only 3.3 c.c. of carbon dioxid instead of 40 c.c. normally present.

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[1] Sassa: "Biochemische Zeitschrift," 1913–14, lix, 362.

[2] Marriott: "Journal of Biological Chemistry," 1914, xviii, 507.

[3] Ringer: *Ibid.*, 1912, xii, 511.

[4] Magnus-Levy: "Archiv für experimentelle Path. und Pharm.," 1901, xlv, 389.

The reduction in the carbon dioxid combining power of the blood and the consequent lowering of the carbon dioxid tension in the alveoli do not appear in the earlier days of acidosis, provided the acids formed be neutralized with ammonia.[1] The withdrawal of alkali occurs later. Rona and Wilenko[2] find that, despite the acidosis, the hydrogen ion concentration of the blood may remain normal on account of the compensation brought about through the removal of carbon dioxid by the lungs and of acids through the urine. Notwithstanding this control over the blood, the authors believe it possible that there may be a local increase of the hydrogen ion concentration in certain cells and tissues.

Concrete cases of blood analyses are offered by Poulton[3] (see p. 221), who reports concerning the blood of 7 diabetic patients. The first 6 possessed a normal blood reaction. One of them (E. M. S.) following the first examination fell into deep coma and twenty-two hours later showed an abnormally high hydrogen ion concentration. E. H., whose blood reaction was similar, was also in deep coma. The first two patients gave no indication of coma, but all the others were drowsy. B. died in coma eighteen hours after the examination of his blood, which had been normal in reaction.

The figures are in part as follows:

PATIENT.	ALVEOLAR CO_2.	P_H.	SODIUM BICARBONATE DAILY.
	Mm.		Grams.
E. R.	38.3	−7.33	0
B. K.	22.0	−7.25	45
F. B.	18.6	−7.36	11
M. T.	16.8	−7.36	6
E. S. M.[1]	15.1	−7.33	8
B.	12.1	−7.35	45
E. H.	8.1	−7.19	60
E. S. M.	7.3	−7.18	45

[1] Münzer: "Zeitschrift für exp. Path. und Therapie," 1914, xvi, 281.
[2] Rona and Wilenko: "Biochemische Zeitschrift," 1913–14, lix, 173.
[3] Poulton: "Journal of Physiology," 1915, l, p. 1.

On the basis of work on a diabetic and comatose boy weighing 32 kg., Magnus-Levy[1] makes the following computation of metabolism. He purposely assumes a high requirement of energy for a lad of this size, or 50 to 55 calories per kilogram, which calls for a total of 1600 to 1700 calories. The boy burned 90 grams of protein and perhaps 200 grams of fat:

	Calories.
90 grams protein = 369 calories 200 grams fat = 1909 calories	= 2278
Deduct 97.5 grams oxybutyric acid, 443 calories Deduct 50 grams urinary sugar, 185 calories	= 628
Calories available	1650

Here we perceive an extreme case of diabetic metabolism in which half the energy contained in protein is excreted in urinary sugar and 20 per cent. of that contained in fat is eliminated in the unburned β-oxybutyric acid.

This, then, is the worst picture of the perverted metabolism in diabetes. Sugar cannot burn, fat burns only as far as β-oxybutyric acid, and as for protein, a part of its amino-acids are converted into sugar and another part into β-oxybutyric acid, neither of which can be burned.

It is notable that the phlorhizinized cancer patient of Stanley Benedict (see p. 455) who had a D : N ratio of 3.66 excreted 37 grams of β-oxybutyric acid and 4 grams of ammonia daily, which shows that the acidosis of diabetes is coincident with a lack of sugar oxidation. In the diabetic C. K. (see p. 478) a fall in the β-oxybutyric acid excretion preceded the break in the D : N ratio (consult p. 271).

Von Noorden[2] and Magnus-Levy[3] report cases in which there was a considerable excretion of aceton bodies in the urine when carbohydrates were burned. For example, one patient eliminated 4.9 grams of β-oxybutyric acid on a day when 40 grams of starch were ingested and burned. There

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[1] Magnus-Levy: "Ergebnisse d. inn. Med.," 1908, i, 385.

[2] von Noorden: "Pathologie des Stoffwechsels," 1907, ii, 77.

[3] Magnus-Levy: "Ergebnisse d. inn. Med.," 1908, i, 404.

are great individual variations. Thus, Stäubli[1] reports concerning a diabetic man whose ordinary mixed diet was changed to one of meat and fat, including 50 grams of bread, the whole containing 3200 calories. After ten days of this diet, during which the sugar output remained nearly constant at 100 grams, the β-oxybutyric acid fell from 37.5 grams daily to nothing. In commenting on his results Stäubli says: "The important factor which causes a more serious condition in the metabolism of a diabetic is the quantity in which carbohydrate is administered in excess of the tolerance for sugar. Damage caused by a continual overworking of the sugar-burning capacity plays a large part in the progress of the disease. The considerable withdrawal of carbohydrates from the diet, even in cases of severe diabetes with high acidosis, exerts an extraordinarily beneficial influence. This can be in part explained by the increased ability to burn sugar on account of the conservation of the body's power in this direction. The improvement in the capacity for sugar combustion exerts on its side a beneficial action on the acidosis."

Turning the attention now to the character of the *total metabolism*, one finds that the severely diabetic patient lives at the expense of protein and fat, both of which are incompletely oxidized by his organism. It follows that the ordinary methods of computation of the respiratory quotients and of the heat value of the protein and fat metabolism must be scrutinized.

Magnus-Levy[2] was the first to make calculations of this sort. Lusk[3] has reviewed the subject and has published a calculation for the value of the respiratory quotient of protein when the urinary D : N ratio is 3.65:

	O_2. Grams.	CO_2. Grams.
Normal oxidation of 100 grams beef protein	138.18	152.17
Deduction for 16.28 gm. × 3.65 which corresponds to 59.41 gm. glucose	63.38	87.15
	74.80	65.02

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[1] Stäubli: "Deutsch. Arch. f. klin. Med.," 1908, xciii, 125.
[2] Magnus-Levy: "Archiv für Physiologie," 1904, 370.
[3] Lusk: "Archives of Internal Medicine," 1915, xv, 939.

Converting the ratio of weights into the ratio of volumes one finds that the diabetic R. Q. for protein is 0.632.

The following calculation shows the caloric value to the organism of 1 gram of urinary nitrogen in diabetes when the D : N is 3.65:

	CALORIES.
Normal value of 1 gm. urinary N....................	26.51
Deduct glucose 3.65 × 3.692 calories...............	13.47
Value of 1 gm. urinary N in diabetes...............	13.04

If large amounts of ammonia are eliminated without being synthesized to urea—which is produced by an endothermic reaction—1 calorie per gram of such extra ammonia nitrogen may be added to the calculated heat production.

If one uses the modified figures to calculate the "non-protein respiratory quotient" in severe diabetes, it is found that the combustion of fat is indicated. A few illustrative calculations are given below, taken from the work of Lusk and of Allen and DuBois:

	D : N.	R. Q.	NON-PROTEIN R. Q.
Phlorhizinized dog........	3.54	0.687	0.704
Diabetic man (G. S.)......	3.5	0.697	0.700
Diabetic man (C. K.).....	3.97	0.687	0.699

The last subject eliminated 71 grams of β-oxybutyric acid on the day of the experiment. It is evident that when allowance is made in the calculations for the altered course of the metabolism of protein in diabetes, the remainder of oxidizable substance possesses approximately the respiratory quotient of fat, which is 0.707.

Theoretically speaking, the subject is more complicated. For example, if ammonia be used to neutralize β-oxybutyric acid, the carbon dioxid with which it would have united to form urea will be eliminated in the respiration and tend to raise the respiratory quotient.

Magnus-Levy has called attention to a possible reduction in the respiratory quotient when β-oxybutyric acid is formed from fat. He estimates that the maximal quantity of β-oxybutyric acid derivable from 100 grams of fat is 36 grams. Under these circumstances, the respiratory quotient for fat would be reduced from 0.707 to 0.669. The case is not so simple, however, for if the 36 grams of acid formed neutralized sodium bicarbonate, 15.23 grams of carbon dioxid would be eliminated.

These relations are shown in the following table:

THEORETIC RESPIRATORY QUOTIENT WITH β-OXYBUTYRIC ACID FORMED FROM FAT

	Oxygen, Liters.	Carbon Dioxid, Liters.	R. Q.
100 gm. fat.	201.9	142.73	0.707
36 gm. β-oxybutyric acid.	34.85	30.96	0.889
	167.05	111.77	0.669
Add for 15.23 gm. CO_2 from $NaHCO_3$.		7.74	
Possible end-result.	167.05	119.51	0.715

Since other bases than sodium bicarbonate may be used for the neutralization of β-oxybutyric acid, it is apparent that the exact determination of the theoretic respiratory quotient when this acid is produced in large amounts in human diabetes is at present impossible.

The establishment of the diabetic quotient at the level of 0.69 also throws light on the dogma regarding the conversion of fat into sugar. Pembrey[1] calculated that if olein were in large part converted into glucose the respiratory quotient for the reaction would be 0.281. The actual findings of the respiration measurements carry the refutation of the idea that fat may be converted into sugar.

It may be well to insert a warning against the too literal interpretation of respiratory quotients obtained under grossly abnormal circumstances. This may be illustrated by the experiments of Porges and Salomon,[2] who ligated the abdominal aorta and the inferior vena cava just below the diaphragm in depancreatized dogs, thereby cutting off the blood-supply to the abdominal organs and probably eliminating half the normal

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[1] Pembrey: "Journal of Physiology," 1901–02, xxvii, 71.

[2] Porges and Salomon: "Biochemische Zeitschrift," 1910, xxvii, 143.

quantity of blood from the circulation. Under these circumstances the respiratory quotient rose to unity and the authors concluded that the diabetic organism could oxidize glucose. This doctrine was refuted by Murlin, Edelmann, and Kramer,[1] who showed that the high respiratory quotient was merely incident to the elimination of carbon dioxid from the blood itself.

One by one the bulwarks of the doctrine of the conversion of fat into glucose have been shattered, and it may now be relegated to the realm of scientific superstition.

Among the earliest investigations of Pettenkofer and Voit[2] was a respiration experiment on a diabetic individual. The authors compared the metabolism of a diabetic with that of a normal man, as indicated in the following table:

COMPARISON OF A NORMAL AND A DIABETIC MAN

	Grams. in the Food.	Grams Burned in the Body.
Healthy man, Protein	120	120
" " Fat	112	83
" " Sugar	344	344
Diabetic man, Protein	107	158
" " Fat	108	158
" " Sugar	337	0
(337 grams of sugar in the urine.)		

It is seen here that the fat and protein metabolism are increased in order to compensate for the non-combustion of the sugar. Several years later, on the basis of these experiments, E. Voit calculated that a diabetic on a moderate mixed diet yielded 1015 calories per square meter of surface, while the normal individual of similar build produced 1020 calories.

The diabetic condition, therefore, does not involve a decrease in the quantity of energy produced, but only an alteration in the source of the energy.

In 1910 DuBois and Veeder[3] published experiments accomplished with Pettenkofer-Voit respiration apparatus in Kraus's clinic at Berlin, which showed that a diabetic patient

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[1] Murlin, Edelmann, and Kramer: "Journal of Biological Chemistry," 1913–14, xvi, 79.

[2] Pettenkofer and Voit: "Zeitschrift für Biologie," 1867, iii, 380.

[3] DuBois and Veeder: "Archives of Internal Medicine," 1910, v, 37.

produced 5 per cent. more heat than a normal man of the same size, the food intake and the amount of muscular activity being the same in both.

Rubner[1] found the metabolism of a fasting dog was the equivalent of 477.8 calories per day, which rose to 510.4 calories after the administration of phlorhizin, an increase of 7 per cent. This increase Rubner rightly attributed to the specific dynamic action of the increased protein metabolism. Lusk[2] has reported an increase in the heat production of 70 per cent. after administering phlorhizin to a dog.

The same influences are active in the depancreatized dog, the heat production being increased 42 per cent., according to Falta, Grote and Staehelin, and Murlin and Kramer.[3]

In the phlorhizinized man of Stanley Benedict (see p. 455) the protein metabolism did not increase as happens in other species, and it is therefore open to question whether there was any increase in his total energy production.

The question of the total energy production in the human diabetic has been extensively studied by Benedict and Joslin[4] and by Allen and DuBois.[5] Whatever of criticism may be found in the following lines, it is to be borne in mind that there is no question of the absolute accuracy of all of this work; the criticism only regards the interpretation. Pflüger has truly stated that criticism is the mainspring of every advance and the Altmeister added, "deshalb übe ich es."

Lusk[6] criticized the first publication of Benedict and Joslin and computed that the average increase in metabolism was not 15 per cent. above the normal, as was stated, but did not exceed 5 per cent. The second publication of Benedict and Joslin maintained that there was an increase of between

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[1] Rubner: "Gesetze des Energieverbrauchs," 1902, p. 370.

[2] Lusk: "Journal of Biological Chemistry," 1915, xx, 598.

[3] Falta, Grote, and Staehelin: "Hofmeister's Beiträge," 1907, x, 199. Murlin and Kramer: "Journal of Biological Chemistry," 1913, xv, 380.

[4] Benedict, F. G., and Joslin: "Metabolism in Diabetes Mellitus," 1910; "Metabolism in Severe Diabetes," 1912.

[5] Allen and DuBois: "Archives of Internal Medicine," 1916, xvii, 1010.

[6] Lusk: "Science," 1911, xxxiii, 434.

15 and 20 per cent. in patients suffering from diabetes, and attributed the increase to acidosis.

The establishment of an accurate method of determining the basal metabolism of normal men through the labors of DuBois has given a method of interpretation of metabolism results which has not heretofore been available. If the height-weight chart of DuBois be used to obtain the surface area and be applied to the diabetic cases and normal controls of Benedict and Joslin ("Severe Diabetes," Table 132), the following calculations may be made:[1]

	Per Cent.
Average variation from normal of 20 controls..........	−8.6
Average variation from normal of 19 diabetics.........	+2.0

The increase in metabolism is, therefore, 2 per cent. above the true normal, but 11 per cent. above the normal controls selected by Benedict and Joslin. This selection may have been justified, for in order to choose individuals who were like the diabetic patients, emaciated controls were indicated and such show a subnormal basal metabolism. Allen and DuBois have pointed out that herein lies the fundamental cause of the divergency in viewpoint. These authors have published a summary of the carefully investigated cases of diabetes mellitus, 26 in all. They found that the basal metabolisms of one-half of these were within the normal range of ±10 per cent.; 9 cases showed increases of 11 to 23 per cent. above the normal basal. Of these cases which manifested a higher metabolism, 3 had severe, 2 marked, 1 moderate, and 3 little or no acidosis. The patient who showed the greatest rise in metabolism had very slight acidosis. Four patients showed metabolisms of between 14 and 19 per cent. below the normal. Of the 17 patients whose basal metabolisms were normal or below the normal, 8 manifested very severe acidosis. The conclusion follows that acidosis cannot be the immediate cause of the increased metabolism when this is found in diabetes.

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[1] Allen and DuBois: *Loc. cit.*

In their analysis Allen and DuBois considered for the first time the factor of emaciation. They call attention to Magnus-Levy's[1] description of a neurasthenic youth who had partially starved himself for a year or more. On entrance to the hospital he was "skin and bones." During the first experimental period he was given his former dietary containing 700 to 800 calories daily and was then given abundant food.

Date.	Weight in Kg.	Calories per Hour.	Calories per Sq. M. per Hour.	Relationship of Metabolism to Average Normal of 39.7.	Remarks.
Nov. 16 to 21...	36.2	34.8	26.6	−33%	Low diet.
Nov. 23 to Dec. 9	38.0	44.9	33.0	−17%	Liberal diet.
Mar. 13 to May 8	52.2	61.9	40.5	+ 2%	Liberal diet.

These valuable data indicate that if a man whose metabolism is normal has been reduced in weight by 30 per cent., his metabolism when he is fed with a low dietary may be reduced 44 per cent. below the actual normal level, or 33 per cent. below, as measured by the normal per square meter of surface. If a liberal diet be given at this juncture, the total heat production is 26 per cent. below the actual normal, or 17 per cent. below if recorded on the basis of surface area. This leads to the query whether basal metabolism of the emaciated diabetic is not really below that of a normal man.

Among the cases cited by Allen and DuBois there are 6 who show an emaciation of over 20 per cent., as follows:

Case.	Urinary N per Day, Grams.	Per Cent. Loss from Greatest Body Weight.	Per Cent. Variation from Normal Calories per Sq. M.
I............	14	30	+14*
T............	9–12	28	0
V............	7– 9.5	26	+15
C. K.........	20	27	+ 3
G. S..........	11–15	31	− 5
W. G.........	14–20	42	−15
Average.....	....	....	+ 3

* Nervous individual.

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[1] Magnus-Levy: "Zeitschrift für klin. Med.," 1906, lx, 177.

It is evident that if the metabolism of a normal man, who through emaciation has lost 30 per cent. of his body weight, is 33 per cent. (or when well nourished 17 per cent.) below the normal level of metabolism, then the emaciated diabetic has in reality a higher heat production than he would have had if he had been free from diabetes. This is emphatically shown in the case of C. K., soon to be more fully described. This individual, who had diabetes in a severe form, subsequently became entirely free from sugar and manifested a high degree of tolerance for carbohydrate. The metabolism of the different periods may thus be summarized:

Condition.	Weight.	Urine.	R. Q.	Per Cent. Loss from Greatest Body Weight.	Per Cent. Variation from Normal Calories per Square Meter of Surface.
	Kg.	N. Gm.			
C. K.: Severe diabetes....	56.7	36.4	0.687	27	+15
Severe diabetes....	56.5	20.0	0.707	27	+ 3
Recovery..........	45.8	..	0.92	43	−36

It is evident that in this emaciated individual the metabolism would have been lower in the first instance had he not been diabetic. The high protein metabolism would sufficiently account for the increased total heat production in this patient, although in some other instances of increased metabolism in diabetes this factor does not apparently always suffice to explain the increase. The frequent presence of lipemia (see p. 252) may explain in part the increased metabolism. The onset of diabetes in this case was very rapid. Nowhere in the literature is the protein metabolism in diabetes mentioned as being so high, and in no other case are the results of metabolism experiments so nearly akin to those obtained in experimental animals.

A preliminary report of the patient C. K. of Geyelin and DuBois[1] gives details of his metabolism in a table which is reproduced on page 478.

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[1] Geyelin and DuBois: "Journal of the American Medical Association," 1916, lxvi, 1532.

CLINICAL AND EXPERIMENTAL DATA IN CASE OF C. K.

Date.	Food Intake, Gm.			Output, Glucose, Gm.	Urine, N, Gm.	D : N Ratio.	Beta-oxybutyric Acid, Gm.	Blood CO₂, Mm. Hg.	Blood Sugar, Per Cent.	Average R. Q.	Average Non-protein. R. Q.	Average Calories per Hour.	Average Calories per Sq. M. per Hour, Linear Formula.[1]	Weight, Kg.
	Carbo-hydrates.	Protein.	Fat.											
1915														
Dec. 8–9	0	0	0	74.9	27.9	2.68	43.7	30.4	0.313					
Dec. 9–10	0	0	0	78.3	29.8	2.61	34.6	....	....	....	....	....	....	57.4
Dec. 10–11	0	0	0	74.2	24.8	2.05	....	26.6	0.340	....	....	....	....	57.8
Dec. 11–12	41.5	17.5	17.7	108.0	30.6	2.17	60.0	21.1	0.312	....	....	....	....	58.2
Dec. 12–13	50.	50.1	69.6	112.0	34.5	1.8	53.0	22.7	....	....	....	....	....	56.7
Dec. 13–14[2]	50.	55.2	58.5	118.7	35.4	1.92	57.9	22.5	....	....	....	....	....	57.0
Dec. 14–15	53.3	58.	51.2	118.5	37.73	1.73	55.2	....	....	....	....	....	....	57.2
Dec. 15–16	23.5	118.6	41.0	167.9	36.37	3.97	70.8	19.95	....	0.687	0.699	81.86	45.7[3]	56.7
Dec. 16–17	0.4	99.	5.6	153.4	38.27	4.01	75.1	19.6	....	0.714	0.743	76.43	42.6[3]	56.8
Dec. 17–18	0.4	39.4	2.9	140.29	36.29	3.87	87.38	35.4	....	....	..	....	....	57.0
Dec. 18–19	0	0	0	55.14	20.01	2.76	58.52	35.4	0.150	0.707	0.706	73.18	40.8	56.5
Dec. 19–20	0	0	0	44.25	16.72	2.65	56.84	40.7	....	....	....	....	....	57.2
Dec. 20–21	1.0	10.	0	35.34	14.07	2.44	41.17	52.5	0.177	0.721	0.718	66.33	37.0	56.0
Dec. 21–22	1.6	20.	0	39.73	14.4	2.65	26.21	....	0.170	....	....	....	....	56.6
Dec. 22–23	5.6	21.	0.1	25.97	18.25	1.12	10.95	52.8	0.181	0.734	0.728	62.82	35.9	54.3
Dec. 23–24[4]	0	0	0	17.01	10.43	....	....	46.3	0.206	....	....	....	....	54.9
Dec. 24–25	0	90.	15.8	15.16	18.32	....	....	46.2	....	....	....	....	....	53.0
Dec. 25–26	0	90.	15.8	32.75	32.70	....	....	40.9	....	....	....	....	....	53.4
Dec. 26–27	0	0	0	10.4	14.28									
Dec. 27–28	0	0	0	0	10.50	....	....	....	....	....	....	....	....	52.6
Dec. 28–29	0	0	0	0	9.05	....	0.241	40.95	0.195	....	....	....	....	52.3
Dec. 29–30	0	51.9	7.9	?	13.79	....	....	....	....	....	....	....	....	52.6
Dec. 30–31	0	0	0	+	13.72	....	....	....	....	....	....	....	....	52.3
1916														
Jan. 31–1	0	0	0	0	8.78	....	....	....	....	....	....	....	....	51.2
Feb. 16[5]	....	....	....	0	....	0	0	....	....	0.915	0.073	42.06	25.4	45.8
Mar. 8[5]	....	....	....	0	....	0	0	....	....	0.860	0.872	50.02	29.1	48.3

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[1] Average basal normal 39.7 calories per square meter per hour.

[2] Transferred to Bellevue Hospital.

[3] After meals which might cause increase in metabolism of 5 to 10 per cent. above basal.

[4] Returned from Bellevue Hospital.

[5] Transferred to Bellevue Hospital. Liberal diabetic diet the days before these calorimeter observations.

On the fifth day of a preliminary fast the D : N ratio of this man was 2.95. Then for four days he was given a mixed diet, moderate in quantity. After this followed a diet containing about 100 grams of protein and the D : N rose to 3.97, 4.01, and 3.87 on three successive days. On the first of these days there was distinct drowsiness; there were 36.4 grams of nitrogen in the urine after an intake of 19 grams in the food; 71 grams of β-oxybutyric acid were eliminated in the urine or about the quantity which could have arisen from the oxidation of fat during the period; the carbonic acid tension in the blood was one-half the normal, and the respiratory quotient was 0.687. The metabolism presented the picture of complete diabetes (see p. 469). Several who saw the patient pronounced the outlook hopeless. Joslin, who happened to be in New York at the time, gave a favorable prognosis. This prognosis was correct. A period of fasting interrupted by days of very low diets resulted in the complete disappearance of glucose and of high nitrogen elimination in the urine within ten days, and on the eleventh day only 0.2 gram of β-oxybutyric acid was eliminated.

Joslin has for a long time privately informed the writer that he would not place a patient upon a diet consisting of protein and fat alone on account of the deleterious effects which might be produced, and he has stated in personal conversation that fatal results might ensue if the diet were long continued. The experiment on C. K. as well as one unpublished experiment not here described show most clearly that Joslin is correct as regards the evil effect of even a moderately high protein intake upon the diabetic patient.

The case of C. K. exemplifies the method of modern treatment of diabetes known as the "Allen method." Weintraud,[1] in the clinic of Naunyn, was the first to recommend the interpolation of occasional fasting days for the benefit of the diabetic patient, and Naunyn[2] practised the reduction of the

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[1] Weintraud: "Centralblatt für klinische Medizin," 1893, xiv, 737.

[2] Naunyn: "Zeitschrift für ärztliche Fortbildung," 1908, v, 737.

body weight of the patient, both by interposing single fasting days and by giving 600 grams of green vegetables which contain little nourishment. Allen, however, on the basis of many fasting experiments with depancreatized dogs,[1] obtained information which he was subsequently able to apply to many diabetic patients[2] in the Rockefeller Hospital. It is certain that he was the first to introduce a rigorous régime of fasting until the diabetic patient becomes free from urinary glucose and from acidosis. Frequently whisky was administered as the only nourishment. Benedict and Török[3] were able to reduce the aceton excretion, as well as that of nitrogen and glucose, after administering alcohol to a diabetic. The experiments of Otto Neubauer[4] showed that red wine reduced the sugar output and the acidosis in diabetes, and Allen and DuBois find indications that the administration of whisky favors the oxidation of glucose in the diabetic. Joslin[5] and Allen and DuBois report that during the clearing up of the diabetes in a fasting patient respiratory quotients are found which are higher than could possibly be obtained from the oxidation of body protein and fat alone. This may possibly be due to the oxidation of the accumulated aceton bodies, the respiratory quotient of β-oxybutyric acid being 0.89, an explanation given by Joslin, who has found respiratory quotients in fasting diabetics as high as 0.8.

Although the great majority of diabetic patients are cured by the fasting treatment, so that they may live on a carefully regulated diet without showing glycosuria, still there are some cases that do not yield to such treatment. Joslin[6] has reported concerning 14 such patients who were diabetics of long standing, or very severe or complicated cases.

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[1] Allen: "Glycosuria and Diabetes," Boston, 1913.

[2] Allen: "Journal of the Amer. Med. Assoc.," 1914, lxiii, 939; *Ibid.*, 1916, lxvi, 1525.

[5] Benedict and Török: "Zeitschrift für klinische Medizin," 1906, lx, 329.

[4] Neubauer, O.: "Münchener med. Wochenschrift," 1906, liii, 791.

[3] Joslin: "American Journal of the Medical Sciences," 1915, cl, 485.

[6] Joslin: "Boston Medical and Surgical Journal," 1916, xlxxiv, 371 and 425.

One of the most interesting researches upon diabetes ever accomplished is that of H. O. Mosenthal in Janeway's Baltimore clinic. At this writing the results have not been published, but are presented here by special permission.

The following table shows the results obtained from a fasting diabetic with a D : N ratio closely approximating that found in the phlorhizinized dog, and resembling a phlorhizinized man (see p. 455) both as regards the D : N ratio and in the quantities of ammonia and β-oxybutyric acid eliminated.

DIABETIC PATIENT PRACTICALLY FASTING

(One egg and green vegetables containing 2 to 6 grams carbohydrate per day during last five days. Wh. = whisky; Wi. = wine. Bicarbonate of soda also administered. The D : N is calculated after subtracting ingested carbohydrate.)

Day of Fast.	Glucose.	Nitrogen.	D : N.	β-Oxybutyric Acid.	NH_3-N.	Alveolar CO_2 Tension.	Alcoholic Beverage.
	Grams.	Grams.		Grams.	Grams.	Mm.	C.C.
4	36.9	10.2	3.64	64.9	4.3		
5	40.3	10.8	3.71	66.0	4.5		
6	36.3	9.8	3.46	50.6	4.2	19.5	
7	31.9	9.0	2.89	64.9	3.9		40 Wh.
8	35.1	9.6	3.44	78.0	4.4		24 Wh.
9	38.0	10.5	3.28	111.2	4.4		8 Wh.*
10	34.7	8.9	3.58	106.6	4.0		490 Wi.
11	35.7	8.7	3.68	73.0	4.2	24.6	345 Wi.
12							
13	Death.						

* And 360 c.c. wine.

At the beginning of the investigation the blood sugar of the diabetic was 0.33 per cent., but fell on the eighth and ninth days to 0.25 and 0.24 per cent.

The advent of the Allen fasting treatment seemed at first likely to make it possible to dispense with laboratory records concerning diabetic cases, but it is still necessary in 10 per cent. and perhaps more of the cases to follow the sugar output, and the intensity of the acidosis for these do not invariably diminish.

Joslin's method[2] of applying the Allen treatment is here reproduced:

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[2] Consult Joslin: "The Treatment of Diabetes Mellitus," 1916, p. 243.

Joslin's Summary of Treatment

Fasting.—Fast until sugar free. Drink water freely and tea, coffee, and clear meat broth as desired. *In very severe, long-standing and complicated cases,* without otherwise changing habits or diet, omit fat, after two days omit protein, and halve carbohydrate daily to 10 grams, then fast.

Carbohydrate Tolerance.—When the twenty-four-hour urine is sugar free, add 150 grams of vegetables containing 5 per cent. of carbohydrate and continue to add 5 grams carbohydrates daily up to 20, and then 5 grams every other day, passing successively upward through vegetables containing 5, 10, and 15 per cent. of carbodydrate, fruits containing 5 and 10 per cent. of carbohydrate, potato and oatmeal to bread, unless sugar appears or the tolerance reaches 3 grams carbohydrate per kilogram body weight.

Protein Tolerance.—When the urine has been sugar free for two days, add 20 grams protein (3 eggs) and thereafter 15 grams protein daily in the form of meat until the patient is receiving 1 gram protein per kilogram body weight, or if the carbohydrate tolerance is zero, only $\frac{3}{4}$ gram per kilogram body weight.

Fat Tolerance.—While testing the protein tolerance, a small quantity of fat is included in the eggs and meat given. Add no more fat until the protein reaches 1 gram per kilogram (unless the protein tolerance is below this figure), but then add 25 grams daily until the patient ceases to lose weight or receives not over 40 calories per kilogram body weight.

Reappearance of Sugar.—The return of sugar demands fasting for twenty-four hours or until sugar free. The diet is then increased twice as rapidly as before, but the carbohydrate should exceed half the former tolerance until the urine has been sugar free for two weeks, and it should not then be increased more than 5 grams per week.

Weekly Fast Days.—Whenever the tolerance is less than 20 grams carbohydrate, fasting should be practised one day in seven; when the tolerance is between 20 and 50 grams carbohydrate upon the weekly fast day, vegetables containing 5 per cent. carbohydrate and one-half the usual quantity of protein and fat are allowed; when the tolerance is between 50 and 100 grams carbohydrate the 10 and 15 per cent. vegetables are added as well. If the tolerance is more than 100 grams carbohydrate, upon weekly fast days the carbohydrate should be halved.

Joslin[1] writes, "The advantages of the new treatment are many. It has made attainable the ideals of treatment, namely, a sugar-free and acid-free urine. The standards of the success of treatment are so simple that they are within the reach of the patient. At one stroke the patient is delivered from medicines, patent or otherwise, sham kinds of treatment, gluten breads, and in ninety-nine cases out of a hundred, of alkalies." With his increased knowledge Joslin[2] does not hesitate to carry pregnancy in the diabetic to term.

Joslin found that the ingestion of fructose by a diabetic did not increase the respiratory quotient (see p. 296).

Von Noorden's oatmeal cure has occupied a prominent place in diabetic therapy. Blum[3] denied its specific efficacy and attributed the results to the low protein dietary. Rolly,[4] on the basis of respiratory experiments, concluded that there was no difference in the value of the various forms of starch ingested by the diabetic, and Joslin[5] showed the failure of either oatmeal or potato starch to raise the respiratory quotient in severe diabetes. Allen believes that the significance of the oatmeal treatment lies in the fact that it is usually administered after interpolation of days of green vegetable diets, which constitute virtual starvation, while Joslin states that in the salt content of the oatmeal lies its only benefit. Baumgarten and Grund[6] have separated the

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[1] Joslin: "American Journal of the Medical Sciences," 1915, cl, 489.
[2] Joslin: "Boston Medical and Surgical Journal," 1915, clxxiii, 841.
[3] Blum: "Münchener med. Wochenschrift," 1911, lviii, 1433.
[4] Rolly: "Deutsches Archiv für klin. Med.," 1912, cv, 494.
[5] Joslin: "Archives of Internal Medicine," 1915, xvi, 693.
[6] Baumgarten and Grund: "Deutsches Archiv für klin. Med.," 1911, civ, 168.

starch and other constituents of oatmeal and have administered them separately to diabetics without improving their condition.

The elimination of β-oxybutyric acid from the system is furthered by the administration of alkalies. Stäubli reports a diabetic who eliminated 34 grams of β-oxybutyric acid daily when the diet contained 60 grams of sodium bicarbonate. This excretion fell to 17 grams on a diet which was free from alkali, and then rose to 45.2 grams on return to 60 grams of bicarbonate. Such treatment with alkali is sometimes highly beneficial, for, as Magnus-Levy observes, the diabetic does not die in coma because of the neutralized acid which is eliminated in the urine, but rather on account of that which is retained in the body which neutralizes the alkalies of tissue and of body fluids.

Von Noorden[1] reports cases of diabetics who have excreted 5 to 6 grams of aceton and 30 to 40 grams of β-oxybutyric acid in a day, and yet have lived comfortably for years.

Alkali therapy has long been considered important in the treatment of diabetes. Bicarbonate of soda up to 200 grams daily has been given. Weiland[2] cites a case in which green vegetables, 200 grams of meat, and 120 grams of sodium bicarbonate were given daily, under which circumstances the urine contained the following ingredients:

	Day.			
	1	2	3	4
Aceton	14.4	11.8	15.1	13.1
β-oxybutyric acid	90.8	68.4	105.9	90.7
Glucose	138.9	132.0	197.0	89.6
Nitrogen	19.3	15.0	25.0	15.2
Ammonia	1.3	1.1	2.9	1.9

It is evident that, despite the high acidosis, the ammonia is kept at a low level on account of the large amount of alkali administered.

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[1] von Noorden: von Leyden's "Handbuch der Ernährungstherapie," 1904, ii, 253.

[2] Weiland: "Zeitschrift für ex. Path. und Ther.," 1912–13, xii, 116.

Murlin[1] has obtained results which indicate that if depancreatized dogs be given alkali they are able to oxidize some glucose. This accords with the idea that diabetes is the result of acidosis (see p. 261). Whether alkali therapy, if applied still more rigorously than heretofore practised, will enable the diabetic patient to oxidize glucose is a question raised by these experiments.[2]

Nothing except dieting affords permanent relief in diabetes. Opium is said to reduce the sugar output in cases bordering on the severe type.[3] The cause of this action is unknown. Experiments inaugurated upon an individual having the 3.65 : 1 ratio might indicate whether its effect was really to increase the combustion of sugar or only to reduce the general metabolism. The ingestion of extracts of different organs does not apparently influence the sugar excretion. Laboratory investigations of the glycolytic power of pancreas extracts have been very numerous, but have failed to give striking results. It is possible that the supposed enzyme or activating substance is extremely sensitive to a change in normal conditions. Mandel and Lusk gave large quantities of yeast to a diabetic man without changing the D : N : : 3.65 : 1, which shows that the enzymes of yeast are not able to penetrate the intestinal wall so that they may replace the natural ferment of the organism.

Raulston and Woodyatt[4] made an intravenous transfusion of blood from a normal man into a diabetic individual, with aggravation of all the symptoms in the latter.

Minkowski[5] discovered that fructose largely reduced protein metabolism in the case of depancreatized dogs. This led to the wide-spread use of fructose in diabetes. Mandel and Lusk, however, found that the increase of sugar in the urine of their diabetic man, after giving 100 grams of fructose,

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[1] Murlin and B. Kramer: "Journal of Biological Chemistry" 1916, xxvii, 517.

[2] Murlin: *Ibid.*, 1916–17, xxviii, 289.

[3] von Noorden: "Diabetes," 1905, p. 158.

[4] Raulston and Woodyatt: "Journal of the Amer. Med. Assoc.," 1914, lxii, 996.

[5] Minkowski: *Loc. cit.*, p. 131.

was 80 per cent. of the sugar ingested. The fructose had no effect whatever on protein metabolism.

Von Noorden[1] confirms this observation. He believes that fructose is normally produced in metabolism and is normally burned. In very rare cases, called levulosuria, fructose alone appears in the urine. One case of complete intolerance for fructose has been reported.[2]

The negative results as regards the value of fructose were especially interesting in the case of Mandel and Lusk. This diabetic medical student was confident of the efficacy of fructose on account of opinions expressed by the writer in his lectures. On the days of fructose ingestion the patient's spirits revived, his strength, measured on the ergograph, decidedly improved, and his companions remarked upon the benefit received, all of which shows that subjective sensations are not to be used as scientific criteria. Stäubli[3] states that administration of fructose reduces the diabetic's tolerance for glucose.

In this connection it may be mentioned that *d*-glucuronic acid and pentoses have a bearing on carbohydrate metabolism. A large variety of substances (camphor, chloral, turpentine) form syntheses with glucuronic acid in the organism, and corresponding glucuronates are then eliminated in the urine. At first glance glucuronic acid appears to be the preliminary oxidation product of glucose, as is suggested by the following equation:

$$\underset{\text{Glucose.}}{OCH(CHOH)_4CH_2OH} + O_2 = \underset{\text{Glucuronic acid.}}{OHC(CHOH)_4COOH} + H_2O$$

However, Mandel and Jackson[4] administered camphor to fasting dogs for several days and noted the excretion of glucuronic acid. On giving large quantities of glucose the protein metabolism fell and with it the glucuronic acid elimination; and on giving the animal chopped meat the quantity of

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[1] von Noorden: *Loc. cit.*, p. 50.

[2] Neubauer: "Münchener med. Wochenschrift," 1905, lii, 1525.

[3] Stäubli: "Deutsches Archiv für klin. Med.," 1908. xciii, 125.

[4] Mandel and Jackson: "American Journal of Physiology," 1902, viii. Proceedings of the American Physiological Society, p. xiii.

campho-glucuronic acid in the urine was correspondingly increased. It may be safely inferred that glucuronic acid is produced solely in the intermediary metabolism of protein. For the large literature on this subject, and also on the pentoses, the reader is referred to other sources.[1]

Pentoses, which are sugars containing 5 atoms of carbon, have been detected in animal and vegetable tissue. Hammarsten found a pentose in the nucleoprotein of the pancreas. Neuberg showed that this pentose and the one obtained from nucleoprotein in the liver is *l*-xylose.[2] Grund[3] has found pentoses in all organs of the body, particularly in those rich in nuclear material.

Salkowski and Neuberg have shown that *l*-xylose may be derived through ferment action on *d*-glucuronic acid. Salkowski was the first to detect a pentose in the urine, and this Neuberg has shown to be *i*-arabinose. The elimination of pentoses in the urine may accompany diabetes, but in extremely rare cases a simple pentosuria occurs in which pentose is the only sugar appearing in the urine.

Luzzatto[4] reports such a case in which the elimination of arabinose was independent of diet or mental or muscular effort. Luzzatto believes the pentose in this case to have been *l*-arabinose. Neuberg finds that in the normal rabbit *l*-arabinose is more readily burned than *d*-arabinose. Luzzatto's case could be explained by supposing that the body had lost its normal power to burn *l*-arabinose as normally produced in metabolism.

Levene and La Forge[5] suggest the probable presence of *d*-ribose in the urine of one individual with pentosuria.

Pentosuria is occasionally discovered in the routine of life insurance examinations. So far as is known it does not indicate danger to general health.

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[1] Neuberg: "Ergebnisse der Physiologie," 1904, iii, 1 Abtheilung, p. 373.

[2] See also Zerner and Waltuch: "Biochemische Zeitschrift," 1913, lviii, 410; Levene and La Forge, "Journal of Biological Chemistry," 1914, xviii, 319.

[3] Grund: "Zeitschrift für physiologische Chemie," 1902, xxxv, 111.

[4] Luzzatto: "Hofmeister's Beiträge," 1905, vi, 87.

[5] Levene and La Forge: "Journal of Biological Chemistry," 1913, xv, 483.

Cremer,[1] in a series of excellent experiments, has shown that a vegetable pentose, such as rhamnose, may be burned in a rabbit and spare an isodynamic equivalent of fat. In one rabbit, on a fasting day, the metabolism amounted to 129.1 calories (protein, 22.5, and fat, 106.6), and on the day when rhamnose was given to 128.4 calories (protein, 21.36; fat, 32.9, and rhamnose, 74.11).

Lindemann and May[2] found that 90 grams of rhamnose could be used by a normal man. When, however, rhamnose was given to a diabetic individual whose urine had been sugar free, sugar appeared in the urine. In cases of severe diabetes reported by von Jaksch[3] it was found that rhamnose, arabinose, and xylose tended to increase the protein metabolism, and hence the sugar output, and also brought about diarrhea. The use of pentoses in diabetes has, therefore, not been successful. The pentoses—rhamnose, arabinose, and xylose—are not convertible into glucose in the organism.[4]

Opie[5] was the first to establish a connection between changes in the islands of Langerhans of the pancreas and the cause of diabetes. Janeway and Oertel,[6] von Noorden, and others, have reported autopsies on cases of severe diabetes in which the pancreas appeared perfectly normal. It is not always possible to observe with the microscope the cause of pathologic change in function.

Allen[7] found degeneration of the islands, which was accompanied by diabetes, after the removal of nine-tenths of the pancreatic tissue in the dog, and Homans[8] reports that the removal of three-fourths of the pancreatic tissue in the cat produces one of two results, either a disappearance of secretory granules in the islands of Langerhans with suggestive evidence

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[1] Cremer: "Zeitschrift für Biologie," 1901, xlii, 428.
[2] Lindemann and May: "Deutsches Archiv für klin. Med.," 1896, lvi, 283.
[3] von Jaksch: *Ibid.*, 1899, lxiii, 612.
[4] Brasch: "Zeitschrift für Biologie," 1908, l, 113.
[5] Opie: "Journal of Experimental Medicine," 1901, v, 397.
[6] Janeway and Oertel: "Virchow's Archiv," 1903, clxxi, 547.
[7] Allen: "Glycosuria and Diabetes," Boston, 1913.
[8] Homans: "Journal of Medical Research," 1914, xxx, 49.

of overactivity and without diabetes; or, occasionally, a degeneration of the islands of Langerhans without disturbance of the remaining acinous tissue, but accompanied by fatal diabetes.

On autopsy in diabetes large quantities of fat are frequently found in the liver and muscles. The same is observed in chloroform narcosis when sugar appears in the urine, in anemia, and after respiration of rarefied air, where lactic acid is eliminated in the urine (p. 423), and in phosphorus- and arsenic-poisoning, in acute yellow atrophy, in pernicious vomiting of pregnancy, in eclampsia and in cyclic vomiting in children, which are similarly accompanied by an elimination of lactic acid. These phenomena are always associated with an increased protein metabolism and an increased ammonia and amino-acid output in the urine.[1] Fat likewise appears in the mammary glands during lactation (see p. 396).

Virchow assumed a fatty degeneration of protein in which the tissue protein was converted into fat, as distinguished from a fatty infiltration in which body fat passed into the cells. Much of the earlier writing of Voit is pervaded with the theory of a considerable origin of fat from protein (p. 228). The idea of a fatty degeneration of protein in the old sense has been largely overturned by the work of Rosenfeld.[2] He finds that if a dog be starved and then given sheep's fat, and again starved, the ingested fat will be found deposited as sheep's fat in his adipose tissue, while the liver will contain about 10 per cent. of fat, and this characteristic dog fat. If now phosphorus- or phlorhizin-poisoning be induced and the liver be examined, 40 per cent. of fat may be found therein, and this in the form of sheep's fat. Hence, in these cases the fat is simply transported to the liver from the fat deposits of the body. The fat in the blood is largely increased. The fat becomes normal in quantity in the liver twenty-four hours after the

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[1] For literature consult Ewing: "Archives of Internal Medicine," 1908, ii, 476.

[2] Rosenfeld: "Ergebnisse der Physiologie," 1903, ii, I, p. 50.

cessation of the phlorhizin action. It is retransported to the places of fat deposit.

B. Fischer[1] reports a case of coma diabeticum in which the blood-serum contained 23 per cent. of fat. Klemperer and Umber[2] state that of 9 diabetics with acidosis 7 had lipemia. Adler[3] and Imbrie[4] report cases in which the blood-serum contained respectively 29 and 14 per cent. of fat plus cholesterol; of the latter there were 3.1 and 1.5 per cent. in the serum in the 2 cases. Lecithin was absent, and Imbrie found that the fatty acids entering into the composition of the blood fat had an iodin number similar to that of the fatty acids entering into the composition of subcutaneous fat. Hence, the lipemia was due to the mobilization of tissue fat.

A supposed production of fat from protein has long been believed to occur in the ripening of cheese. However, Kondo[5] finds that in the process of ripening cheddar cheese 9 per cent. of the fat content disappears after thirty days and 12 per cent. after forty days.

If a fatty "degeneration" were to be found anywhere, it would certainly be looked for in the dying cells of the liver in phosphorus-poisoning, or in the analogous condition of acute yellow atrophy of the liver. But another explanation avails. Mandel and Lusk[6] have shown that lactic acid disappears from the blood and urine of a phosphorized dog if phlorhizin glycosuria be induced. The writer believes that the lactic acid which occurs is derived from the sugar formed in protein metabolism. In the above case the sugar is removed without conversion into lactic acid. In phlorhizin diabetes, glucose does not burn; in phosphorus-poisoning lactic acid derived from glucose does not burn. In both cases a sugar-hungry cell, or one where carbohydrate is not oxidized, is found, and under these circumstances fat is attracted to the cell, and in

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[1] Fischer, B.: "Virchow's Archiv," 1903, clxxii, 30 and 218.

[2] Klemperer and Umber: "Zeitschrift für klinische Medicin," 1908, lxv, 340.

[3] Adler: "Berliner klin. Wochenschrift," 1909, xlvi, 1453.

[4] Imbrie: "Journal of Biological Chemistry," 1915, xx, 87.

[5] Kondo: "Biochemische Zeitschrift," 1913–14, lix, 113.

[6] Mandel and Lusk: "American Journal of Physiology," 1906, xvi, 129.

larger quantities than can be useful. Wherever sugar freely burns, this fatty infiltration is impossible (p. 249). A reduced local circulation in a portion of the heart may produce anemia of the part, an imperfect local oxidation of lactic acid normally formed, and a fatty infiltration of the locality. The writer offers this hypothesis as his explanation of fatty changes in tissue in general.

A corroborating fact found by Shibata[1] is that, although the amount of fat in the liver is increased in phosphorus-poisoning, the quantity of total fat in the organism is much reduced during the progress of this disease. In cases of fatty infiltration (so-called degeneration) Czyhlarz and Fuchs[2] could find no evidence of an abnormally changed relationship between the quantities of cholesterol and fat present in the diseased tissue.

Medical literature was formerly greatly influenced by the idea of a reduced general oxidation in the body. Except in the case of myxedema which is accompanied by a fall in body temperature, and in some cases of obesity, no such condition occurs. The writer[3] has shown that in phosphorus-poisoning, the classical example of supposed reduced oxidation, there was actually no reduction in the total heat production, but rather an increase. From the fourth day to the sixth of simple fasting in one dog the total metabolism for twenty-four hours averaged 45.2 calories per kilogram, and on the ninth day to the eleventh of fasting which preceded death from phosphorus-poisoning the heat production was 48.8 calories. These results have been confirmed by Hirz.[4]

It is therefore evident that the presence of lactic acid is only a symptom in the group of diseases just mentioned (p. 489), and is no more an indication of a reduction in oxidative power as represented by the total heat production than is the elimination of sugar in diabetes. The abundant ammonia in

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[1] Shibata: "Biochemische Zeitschrift," 1911, xxxvii, 345.
[2] Czyhlarz and Fuchs: *Ibid.*, 1914, lxii, 131.
[3] Lusk: "American Journal of Physiology," 1907, xix, 461.
[4] Hirz: "Zeitschrift für Biologie," 1913, lx, 187.

the urine is used to neutralize the acid produced. The reduction in the amount of lactic acid oxidized raises the total protein metabolism. The deficient deamination which results in the elimination of amino-acids in the urine may possibly be due to the injury of deaminating enzymes by the presence of lactic acid.

It has been stated that the action of phosphorus is to induce autolysis (self-digestion) of the body's protoplasm (Jacoby,[1] Waldvogel[2]), since leucin, tyrosin, glycocoll,[3] phenyl-alanin and arginin,[4] and other amino-acids may be eliminated in considerable quantity in the urine. Wakeman[5] finds a change in the relative amounts of histidin, arginin, and lysin contained in the liver substance after phosphorus-poisoning, arginin in particular being reduced below the quantity found in the liver of the normal dog. Oswald[6] thinks that phosphorus destroys or weakens the anti-autolytic agents of the body. That autolytic enzymes do not gain free control over the cells through the direct influence of phosphorus is proved by the work of Ray, McDermott, and Lusk.[7] These authors found that phosphorus injections raised the protein metabolism of fasting dogs to 250, 260, 283, 248, 183, and 164 per cent. of that of the dog when normal. They contrasted this increased protein metabolism with that obtained in phlorhizin glycosuria, which is represented by increases to 540, 450, 340, and 340 per cent. When, however, they gave phlorhizin and obtained the increased metabolism, and then injected phosphorus, *this was not followed by any marked increase in protein metabolism.* Under these circumstances phlorhizin glycosuria is the predominating factor, removing the glucose produced from protein before it could be converted into lactic acid.

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[1] Jacoby: "Zeitschrift für Physiologische Chemie," 1900, xxx, 174.

[2] Waldvogel: "Deutsches Archiv für klinische Medizin," 1905, lxxxii, 437.

[3] Abderhalden and Bergell: "Zeitschrift für physiologische Chemie," 1903, xxxix, 464.

[4] Wolgemuth: *Ibid.*, 1905, xliv, 74.

[5] Wakeman: *Ibid.*, 1905, xliv, 335.

[6] Oswald: "Biochemisches Centralblatt," 1905, iii, 365.

[7] Ray, McDermott, and Lusk: "American Journal of Physiology," 1899, iii, 139.

Analogous to this is the observation of Sass,[1] who found that under normal conditions strychnin convulsions reduced the titratible alkalinity of the blood on account of the formation of lactic acid, but in depancreatinized dogs this result could not be achieved because lactic acid could not be produced from glucose.

As regards phosphorus-poisoning Araki[2] believes that lactic acid accumulation is due to lack of oxygenation of the tissues caused by a slow heart-beat, but not due to anemia. He does not believe the oxygen deprivation to be very pronounced. The writer offers the explanation that phosphorus may affect the conditions which lead to the oxidation of the lactic acid derived from glucose (see p. 263), and the accumulation of this acid may prevent the action of some of the deaminating enzymes; and, further, its non-combustion may necessitate an increase of protein metabolism.

This theory is strengthened by the discovery of Schryver[3] that the addition of lactic acid favors the accumulation of amino-acids in autolysis of the liver.

Claude Bernard showed that glucose, whether derived from protein or starch, was convertible into glycogen, and this again was changeable into glucose. Present knowledge adds lactic acid to both ends of this chain in showing the following possible progression—lactic acid, glucose, glycogen, glucose, lactic acid (see p. 263).

Quite pertinent to this theoretic discussion is the observation of von Jaksch[4] on a patient who recovered from phosphorus-poisoning, and in whom a desire for carbohydrates marked the beginning of convalescence.

It should also be noted that more carbohydrates must be ingested in cases of hepatic disease to maintain nitrogen equilibrium than are required in health.[5]

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[1] Sass: "Zeitschrift für ex. Path. und Ther.," 1914, xv, 370.
[2] Araki: "Zeitschrift für physiologische Chemie," 1893, xvii, 337.
[3] Schryver: "The Bio-Chemical Journal," 1906, i, 153.
[4] von Jaksch: "Zeitschrift für physiologische Chemie," 1903, xl, 123.
[5] Tallqvist: "Archiv für Hygiene," 1908, lxv, 39.

A curious anomaly of carbohydrate metabolism has been discovered by Underhill[1] following the administration of hydrazin, which he defines as a poison with an almost specific effect upon the cytoplasm of the parenchymatous cells of the liver. It attacks first the cells in the center of the lobules, while phosphorus shows its first effects upon the cells of the periphery. If 50 milligrams of hydrazin per kilogram of animal be given to dogs, the quantity of glucose in the blood and of glycogen in the liver is greatly reduced and the administration of glucose may cause the death of the animal within twelve hours. Otherwise the dog recovers in five days. Underhill and Murlin[2] found that the administration of hydrazin to fasting dogs increased the respiratory quotient. An increased oxidation of carbohydrate, therefore, probably explains the diminished blood-sugar content and the disappearance of glycogen from both liver and muscles. Hydrazin was without influence upon the level of the basal metabolism.

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[1] Underhill: "Journal of Biological Chemistry," 1911–12, x, 159.

[2] Underhill and Murlin: *Ibid.*, 1915, xxii, 499.

CHAPTER XVII

METABOLISM IN NEPHRITIS, IN CARDIAC DISEASE, AND IN OTHER CASES INVOLVING ACIDOSIS

In 1821 Prevost and Dumas[1] observed that if the kidneys of a dog be extirpated, urea accumulates in the blood. This observation led to the discovery by Bright in 1836 that the amount of urea in the blood of nephritic patients was abnormally high.

Using more accurate methods, Folin[2] finds that when a low protein dietary is taken the normal figures for total non-protein nitrogen in the blood of a man are 22 to 28 milligrams per 100 c.c. of blood, of which 11 to 14 milligrams are in the form of urea. The maximum amount of non-protein nitrogen in a normal person is not usually above 40 milligrams per 100 c.c.[3] Sometimes after protein ingestion in nephritis the non-protein nitrogen does not increase in the blood; in other cases there is a considerable rise. The increased level of urea in the blood is a compensatory reaction to a diminished power of excretion by the kidney.[4]

Emphasis has been laid upon a negative nitrogen balance as indicating a retention of urea by the nephritic patient, but such a retention is susceptible of two interpretations. Thus, Mosenthal and Richards[5] have given patients with moderately severe chronic interstitial nephritis diets containing between 16 and 47 grams of nitrogen and have observed nitrogen reten-

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[1] Prevost and Dumas: "Ann. de chemie et de phys.," 1821, xxiii, 90.

[2] Folin, Denis, and Seymour: "Archives of Internal Medicine," 1914, xiii, 224.

[3] For the complete chemical and physical analysis of blood in 30 normal cases consult the important work of Gettler and Baker: "Journal of Biological Chemistry," 1916, xxv, 211.

[4] McLean: "Journal of Experimental Medicine," 1915, xxii, 366.

[5] Mosenthal and Richards: "Archives of Internal Medicine," 1916, xvii, 329.

tion. Had this retention been in the form of non-protein nitrogen, the blood would have contained between 78 and 148 milligrams of such nitrogen, but the actual values never rose above 38 milligrams. Davis and Foster,[1] however, find that nitrogen retention under these circumstances may take place in the liver and muscle in the form of non-protein nitrogen. The very ill patients were benefited by large water ingestion.

Henderson and Palmer[2] describe cases of nephritis in which the volume of the urine is large, the titratable acidity high, but in which the total acid elimination is decreased because of a greatly reduced elimination of ammonia. They conclude that this points to a condition of acidosis of renal origin. As a matter of fact, Peabody[3] has discovered that the acidosis of nephritis is due to a retention of non-volatile acids which would ordinarily be removed by the kidney.

Peabody, Aub, and DuBois, in experiments yet to be published, have made investigations concerning the metabolism of 10 patients suffering from severe nephritis which show that most of the individuals had normal basal metabolisms. In the presence of greatly decreased alkalinity and of a high content of non-protein nitrogen in the blood the total heat production showed no variation from the normal.

Tachau[4] finds that in nephritis the loss of nitrogen by way of the sweat induced by an electric light bath is not material, but that the loss of sodium chlorid may reach 2 grams per hour and may reduce an edema.

In patients who manifest marked evidence of circulatory disturbances Foster[5] shows that there is an increase in the quan-

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[1] Davis and Foster: "Proceedings of Soc. for ex. Biol. and Med.," 1915, xiii, 33.

[2] Henderson, L. J., and Palmer: "Journal of Biological Chemistry," 1915, xxi, 37.

[3] Peabody: "Archives of Internal Medicine," 1914, xiv, 236; *Ibid.*, 1915, xvi, 955.

[4] Tachau: "Deutsches Archiv für klinische Medizin," 1912, cvii, 305.

[5] Foster, N. B.: "Archives of Internal Medicine," 1915, xv, 356.

tity of non-protein nitrogen of the blood, even in the absence of nephritis.

Peabody, Meyer, and DuBois[1] studied 16 patients with cardiac and cardiorenal disease by the methods of direct and indirect calorimetry. The two methods agreed within 1.9 per cent. There was no abnormal deviation of the respiratory quotients as had been announced by several previous investigators. Patients with compensated cardiac lesions or with mild nephritis showed a normal metabolism. Of 12 patients with dyspnea, 9 showed a distinct rise in metabolism, and in 5 of these the increase was between 25 and 50 per cent. above the normal. Two of these 5 patients manifested marked acidosis, as was indicated by a low carbon dioxid tension in the alveolar air. In 2 other patients, whose metabolisms were equally high, there was no significant depression of the alveolar carbon dioxid.

If the dyspnea were accompanied by the production of lactic acid in any of the organs, this might have been the stimulus to the higher metabolism observed. The decompensated heart produces slow or insufficient circulation with imperfect oxidation in the tissues, which conditions readily lend themselves to lactic acid formation.

Howland and Marriott[2] describe a type of acidosis which occurs in infants during the course of attacks of severe diarrhea not of ileocolitic type. The usual type of abdominal breathing of the young child is succeeded by one which is both costal and abdominal. There is a greater amplitude in the respirations and they are made with a distinct effort. There is no cyanosis. The condition was first described by Czerny[3] who called attention to the symptoms as resembling those observed in rabbits dying after the administration of mineral acids. Howland and Marriott find that a condition of acidosis

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[1] Peabody, Meyer, A. L., and DuBois: "Archives of Internal Medicine," 1916, xvii, 980.

[2] Howland and Marriott: "American Journal of Diseases of Children," 1916, xi, 309.

[3] Czerny: "Jahrbuch für Kinderheilkunde," 1897, xlv, 271.

is actually present in these children and they were the first to use alkaline treatment in order to rescue them. The acidosis is not due to acetone bodies, from which the blood is free.

The following presents the results of treatment in one of their cases:

	Date.	Alveolar CO$_2$ Tension.	Hyperpnea.	Alkali.
		Mm.		
Case I	22	21	+++	Given.
	23	42	0	Given.
	24	54	0	Stopped.
	24	55	0	
	25	41	0	

In normal infants the carbon dioxid tension is between 36 and 45 mm. and the P_H of the blood is 7.4. In the children with acidosis the P_H of the blood was 7.2. There was also a reduction of the reserve alkali of the blood. There was frequent anuria and the conclusion is drawn that the cause of the acidosis is probably a retention of acid phosphate in the organism.

CHAPTER XVIII

METABOLISM IN FEVER

By fever is generally understood a complex of phenomena the dominant characteristic of which is a rise of body temperature. If the term "fever" be confined simply to the latter aspect, one might classify fevers as follows:

(1) *Physiologic fever*, induced, for example, by immersion in a hot bath at a temperature of 40°, which prevents the normal loss of body heat through radiation and conduction. (2) *Neurogenic fever*, as brought about by the direct stimulation of nerve-cells in the *corpora striata* of the mid-brain. (3) *Non-infective surgical fever*, commonly called *aseptic fever*, due to the resolution of blood-cells or crushed tissue in the organism. (4) *Infective fever*, produced after the infection of the organism by certain bacteria or their products and by some protozoa. Or one may consider fever as being due to infection by bacteria or protozoa, and include all other increases of temperature under the term of *hyperthermia*.

In a previous chapter the mechanism of normal heat regulation has been explained. It was there noted that on a warm, moist day the temperature of a fat individual, when he was working hard, rose considerably above the normal. This effect, if carried to an extreme, results in *sunstroke*, in which the overheating of the body causes a rapid pulse, accompanied by dizziness, delirium, or unconsciousness. But in the great majority of cases the body temperature remains delicately balanced, notwithstanding changes in outside environment, or internal heat production. In the fat person at hard work the condition of increased metabolism is combined with that of difficult discharge of heat. A person placed in a bath at 40° would be subject to conditions where there could be no heat loss, but rather a gain in heat, even though his metabolism were low. In a normal person, therefore, a rise in temperature may be due to increased heat production, with difficulty in discharging it, or a check of heat loss may be the only factor of the higher temperature. In the discussion of fever one must consider two possible causes: (1) an increase in heat production, and (2) a decrease in the facilities for the discharge of heat produced.

It has already been set forth that the metabolism in a cold-blooded animal increases with the temperature of his environment. Warmed tissue metabolizes more material than cooled tissue. It is therefore to be expected that the metabolism in an organism which has been warmed to fever heat will be greater than the normal. This was beautifully shown in the experiments of Pflüger,[1] who subjected both curarized and normal rabbits to external warmth which raised their temperatures. In the animals whose voluntary muscles were paralyzed by curare as the rectal temperature rose from 39° to 41° the oxygen absorption increased 10 per cent. for each degree of temperature increase. In the normal animals the increased metabolism between temperatures of 38.6° and 40.6° was shown by increases of 5.7 per cent. for oxygen and 6.8 per cent. for carbon dioxid for a rise of 1° of temperature.

It has been noted in another chapter (p. 144) that Rubner found in man that a bath at a temperature of 35° had no effect on metabolism, while one at 44° increased the volume of respiration 18.8 per cent., the oxygen absorption 17.3 per cent., and the carbon dioxid elimination 32.1 per cent. Linser and Schmid[2] confirm these results in experiments on two men suffering from *ichthyosis hystrix*, which involved almost complete loss of function of the sweat-glands. The body temperature of these men could be varied by altering the temperature of their living-room between 30° and 38°. The humidity of the

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[1] Pflüger: "Pflüger's Archiv," 1878, xviii, 303, 356.

[2] Linser and Schmid: "Deutsches Archiv für klinische Medizin," 1904, lxxix, 514.

room was from 40 to 50 per cent. The maximum increase in the metabolism of these individuals is represented by a rise in carbon dioxid excretion from 3.8 c.c. per minute and kilogram at the body temperature of 36.2° to 5.3 c.c. per minute and kilogram at 39°. The number of respirations, which were from 12 to 15 per minute at 36°, increased to 20 and 22 at 39°. The total increase in the carbon dioxid output, due to a rise of 3° through simple warming of cells, amounted to 40 per cent.

The next question is of the nature of the materials which are oxidized. It has long been known that urea excretion is abnormally high in fever,[1] and this led to the inquiry whether the rise was merely the result of increased body temperature or was due to toxic influences.

F. Voit[2] found that on artificially raising the temperature of a fasting dog to 40° or 41° for a period of twelve hours there was an increase in nitrogen elimination of 37 per cent. above the normal. Warming for a period of only three hours had slight effect. If, however, the animal were fed with meat and fat, warming increased the protein metabolism only 4 per cent. If the animal were given 30 to 40 grams of cane-sugar no increased metabolism of protein followed the rise in temperature to 41°. It is apparent that the ingestion of protein and carbohydrates may control this rise in protein destruction due to a febrile temperature. F. Voit explains the increase in protein metabolism in hyperthermia as due to the quick combustion of glycogen and the consequent impoverishment of the tissues as regards carbohydrate material. Protein or carbohydrate ingesta furnish the necessary carbohydrate and prevent the hyperthermal rise in protein metabolism.

Careful experiments by Graham and Poulton,[3] conducted in Friedrich Müller's clinic in Munich, have shown that in man a body temperature of 40.2°, brought about by the influence of a steam bath, does not of itself cause an increase in the

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[1] Traube and Jochmann: "Deutsche Klinik," 1855, vii, 511.

[2] Voit, F.: "Sitzungsberichte der Gesellschaft für Morphologie und Physiologie," 1895, Heft ii, p. 120.

[3] Graham and Poulton: "Quarterly Journal of Medicine," 1912, vi, 82.

metabolism of body protein. Three different diets were taken. In experiments I and II the caloric value of the diet was high, with excess of carbohydrate and only a minimal quantity of protein. Diets III and IV were composed chiefly of protein and fat; one with ample calories and high in protein, the other with insufficient calories and only a moderate amount of protein. The results of the experiments may be thus epitomized:

Subject	P.	G.	P.	G.
Experiment	I	II	III	IV
Character of diet	CH+fat.	CH+fat.	Prot.+fat.	Prot.+fat.
Calories in diet	4950	4690	3700	1970
Calories per kg. per day	68	75	50	32
N in diet, grams	1.23	0.91	34.4	12.3
No. of days of diet before experiment	6	6	19	8
± Body N, day before bath	−3.37	−3.00	+1.91	−3.41
± Body N, day of hot bath	−2.88	−2.78	+1.42	−2.45
± Body N, day after bath	−2.85	−2.47	+1.66	−3.22
Maximal body temperature, day of bath	39.3°	40.2°	40.1°	39.7°

In these experiments the abnormally high body temperature was maintained for several hours, and yet there was never any increase in the breakdown of body protein due to the hyperthermia.

It has already been recited (see p. 317) how Kocher, working in the same clinic, found that a walk of 60 kilometers with a consequent doubling of the heat production was without effect upon the protein metabolism even when the output of urinary nitrogen was at a minimal level.

It is evident from these experiments that neither high body temperature nor largely increased heat production has any effect upon the minimal "wear and tear" quota of protein metabolism. The destruction of protein by toxic processes in fever is, therefore, independent of the two factors enumerated, as will be seen later.

If certain portions of the brain be punctured, and particularly the region of the *corpora striata*, a high fever sets in. Here again there is an increased output of carbon dioxid and a rise in protein metabolism. This phenomenon has been recently investigated by Hirsch, Müller, and Rolly,[1] and by Rolly[2] alone. They find that after the "heat puncture" of the corpora striata the liver, blood, and skin become warmer than the muscles, although normally the muscles are warmer than the skin. They find that the heat puncture is effective even in curarized animals, where the muscles are free from nerve stimuli. Rolly finds, however, that the heat puncture is ineffective if the liver of the rabbit has been previously freed from glycogen by strychnin convulsions. Under these circumstances there is no rise in temperature nor concomitant rise in protein metabolism. The inference is that the fever in question is due to nerve impulses which increase the metabolism of carbohydrate in the liver. In infectious fever there is little glycogen in the organism, but that the fever in this case is due to other causes than the rapid combustion of carbohydrates was shown by Rolly, who infected a rabbit, which had been freed from glycogen as above described, with a culture of pneumococci and obtained as great a rise in temperature and protein metabolism as would have occurred had the tissues of the rabbit been rich in carbohydrates. The rise in temperature after puncture of the corpora striata may be termed *neurogenic fever*, and it is like the glycosuria following Claude Bernard's puncture, in that its mechanism is no more invoked in true infectious fever than are the nerve centers in diabetes mellitus (p. 446).

Freund[3] finds that simple heat puncture in the rabbit is still effective after cutting the cord at the level of the second dorsal nerve. It is interesting that this phenomenon of heat puncture, with its increased carbohydrate combustion and an elevation of body temperature between 0.7° and 1.76° in

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[1] Hirsch, Müller, and Rolly: "Deutsches Archiv für klin. Med.," 1903, lxxv, 264.

[2] Rolly: *Ibid.*, 1903, lxxviii, 250.

[3] Freund, H.: "Archiv für exp. Path. und Pharm.," 1913, lxxii, 304.

rabbits and in dogs, is without influence upon the hydrogen ion concentration of the blood.[1]

If the extent of metabolism in infectious fevers be investigated the following state of affairs is discovered. The course taken by the metabolism in toxic fevers is, as a rule, (1) a slight rise in protein metabolism, even before the fever sets in; (2) increased metabolism with heat retention and increased protein destruction; (3) heat production and heat elimination become equal, with the body at a higher temperature level. These factors were illustrated in the experiments of May[2] on fasting rabbits injected with a culture of erysipelas of the pig and in the following experiments of Staehelin.

Staehelin[3] infected a dog by inoculating him with 1.5 c.c. of dog's blood containing surra trypanosomes which are active flagellate parasites. Fever set in on the sixth day after the inoculation and the dog died on the twenty-fifth day. The metabolism due to the infection rose to 88.9 calories per kilogram on the tenth day after inoculation as against a normal of 59.8, an increase of 48 per cent. On this febrile day 26 per cent. of the total energy was yielded by protein; the body lost 2.8 grams of nitrogen, which indicated a high toxic waste. However, all the increase in the heat production did not come from increased protein metabolism, but the fat destruction was also increased, and Staehelin speaks of a toxic waste of fat. He also remarks that the dog remained perfectly quiet during the period of the experiment, but he does not say whether thermal influences which could result in chill were completely excluded. However, he came to the conclusion that in this fever caused by trypanosomes the metabolism was higher than could be explained by the overwarming of the body.

During the last days of life the body temperature fell and with it the amount of the metabolism. The following table gives a partial record of the daily metabolism in this dog:

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[1] Quagliariello: "Biochemische Zeitschrift," 1912, xliv, 162.
[2] May: "Zeitscheift für Biologie," 1894, xxx, 1.
[3] Staehelin: "Archiv für Hygiene," 1904, l, 77.

METABOLISM IN FEVER INDUCED BY SURRA TRYPANOSOMES

Period.	Day after Inoculation.	No. of Days in Period.	Grams N in Food.	Grams N to Body.	Calories in Food.	Calories of Metabolism.	Calories per Kg.	Calories per Sq. M. Surface.	Body Temp.	
									Max.	Min.
I. Normal (average).	..	..	5.67	+0.15	585	510.0	59.8	1027		
II. Inoculation and prodromal	6	6	5.67	−0.18	585	469.3	58.3	982	39.4	38.3
III. 1st of fever	7	4	5.67	−0.40	585	521.4	63.9	1081	39.5	38.3
	8	..	5.67	−0.46	585	556.9	68.2	1154	39.6	37.7
	9	..	5.67	−1.06	585	675.2	81.6	1388	40.1	39.6
	10	..	5.67	−2.80	585	729.3	88.9	1507	39.2	37.9
IV. 2d of fever (average)	11–17	7	4.37	−2.50	451	665.2	83.7	1404		
V. 3d of fever (average)	18–20	3	3.34	−2.52	348	665.0	74.0	1218	40.4	38.5
VI. Final period (average)	21–24	4	—	−4.63	..	521.0	62.0	907	38.8	35.5

Long before these experiments Wood[1] had found an average increase of 23 per cent. (calculated by Welch) in the heat production of fasting dogs after inducing fever; and he also found that mere ingestion of food by a normal dog would cause a greater heat production than fever itself.

Traube,[2] who was the first modern scientific clinician, attributed the cause of fever to a cramp-like constriction of the peripheral arterioles, which prevented the proper distribution of the blood at the surface and therefore hindered the normal cooling of the body. Since Traube's writings on the subject were published the cause of fever has been attributed not to greater heat production, but to a disturbance in the mechanism of the regulation of heat loss. On recalling the fact that the metabolism of a fasting dog may be raised from 100 calories in fasting to 189 calories after giving meat (see p. 234) without any change of body temperature, it becomes evident that the increased heat production in fever cannot alone be the cause of the high body temperature. In fact, as has already been set forth, the rise in the body temperature from failure of the

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[1] Wood: "Fever," Smithsonian Contributions to Knowledge, Washington, 1880.

[2] Traube: "Allgemeine medizinische Central-Zeitung," 1863, xxxii, 410, 426, 810.

physical regulation may of itself explain the increase in heat production.

Senator[1] early recognized that the increase in body temperature took place in consequence of a disturbed relationship between an abnormally high heat production and a heat elimination not correspondingly high. Senator assumed an increase in the production of heat, which Traube did not, and Leyden[2] found a considerable increase of metabolism in fever.

The effect of a cold bath upon a vigorous man is to constrict the peripheral blood-vessels and to increase the heat production. The body temperature, instead of falling, may rise for eight or ten minutes and then sink.[3] If the individual pass from the bath during the earlier minutes the hot blood comes to the surface to be cooled, and the body glows with a red color, the so-called "reaction." This experiment shows that there are factors invoked during the first few minutes which prevent the discharge of the heat produced. One factor must be a general constriction of the peripheral arteries, causing the blood to remain in the heat-producing inner organs of the body. In this experiment, therefore, cooling of the organism is prevented by the mechanism of physical regulation above described, and the mechanism of chemical regulation which reflexly increases heat production.

To combat a rise in temperature, however, the only means available is the physical regulation—*i. e.*, the change in the distribution of the blood and the production of sweat. If these avenues of heat loss be diminished or shut off, heat accumulates within the body and the temperature rises. Why an increase in heat production of 89 per cent. may not cause a rise in temperature in a normal animal has already been explained; whereas, a high fever may be accompanied by much less of an increase in metabolism. The cause of the fever must, there-

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[1] Senator: "Allgemeine medizinische Central-Zeitung," 1868, xxxvii, 926; and "Untersuchungen über die fieberhaften Prozesse," Berlin, 1873.

[2] Leyden: "Deutsches Archiv für klinische Medizin," 1870, vii, 536.

[3] Lefèvre, J.: "Comptes rendus soc. biol.," 1894, xlvi, 604.

fore, be a diminution in the ability to discharge the heat produced.

In further support of this Senator has shown that the fever following pus injections in a dog begins with a retention of heat within his body. Nebelthau[1] found in a rabbit that during the first twelve hours of infection in which the temperature rose from 38.6° to 40.1° the discharge of heat was but 96.3 per cent. of that of the previous period. Assuming the heat production to have been the same in these two periods, then the retention of heat would account for the pathologic increase in temperature. At a later stage the discharge of heat rose to equalize its production at the higher temperature.

It is evident from this discussion that a problem of great interest is involved in the following three questions: (1) Does an increased metabolism precede a rise in body temperature? (2) Do increases in metabolism and body temperature occur simultaneously? (3) Does the rise in body temperature precede the increase in metabolism? The questions can only be answered by simultaneous determinations of the heat production by the methods of direct and indirect calorimetry, accomplished in short periods and using most exact methods and technic.

Such work was accomplished by Coleman and DuBois[2] in their studies concerning typhoid fever. Their results are presented in the form of a chart (Fig. 26).

In every one of these cases there was a rising body temperature. In every case but one an increase in heat production accompanied the rising body temperature; and the heat elimination, though not equal to the heat production, rose to meet the needs of the higher level of metabolism. The major part of the evidence, therefore, points to an increase in the metabolism which is coincident with an elevation of body temperature when determinations are made in hourly periods.

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[1] Nebelthau: "Zeitschrift für Biologie," 1895, xxxi, 353.

[2] Coleman and DuBois: "Archives of Internal Medicine," 1915, xv, 887.

In one instance (Morris S., October 24th) the heat production and heat elimination both fell notwithstanding a rising body temperature. This could only have been accomplished through an alteration in the apparatus for the elimination of

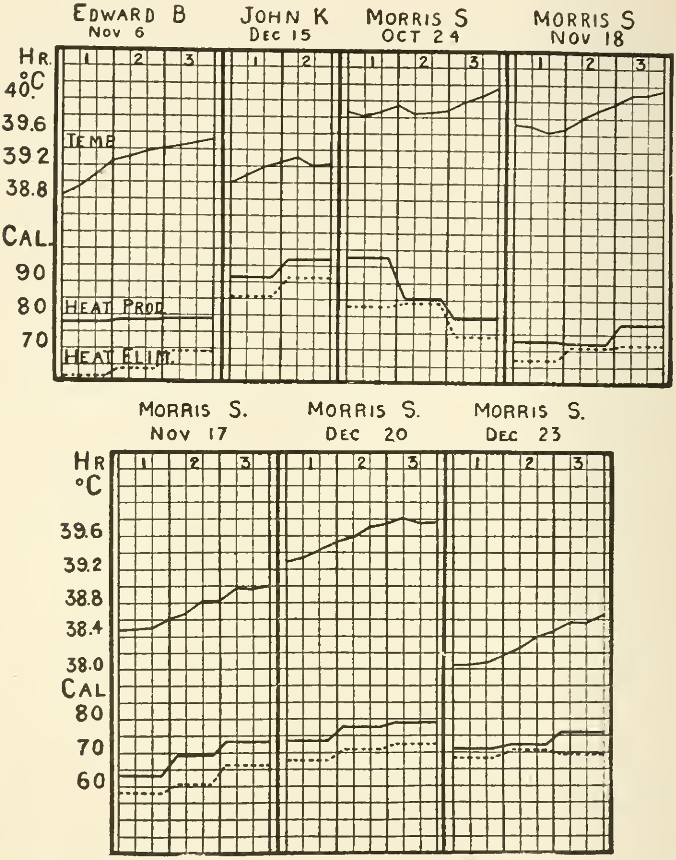

Fig. 26.—Curves showing the relationship and heat elimination in fever Rising temperature. The uppermost line shows the rectal temperature as measured every twenty minutes. The heavy continued line represents the heat production in hourly periods as determined by the method of indirect calorimetry. The dotted line gives the heat elimination as determined by the measurement of the calories of radiation, conduction, and vaporization. The difference between the levels of these two lines represents the heat stored in the body as the temperature rises. Note the fact that in every case except one the heat elimination increases with a rising temperature.

heat from the body, in the sense of Traube's analysis of fever.

Coleman and DuBois also cite experiments which show that when the body temperature is constant in high fever the heat production and heat elimination are equal to each other, and when the body temperature falls the heat elimination rises above the heat production, while the amount of the latter may or may not fall.

Coleman, Barr, and DuBois have recently noted in the case of a man suffering from erysipelas that a fall in body temperature of 1° C. during sleep in the calorimeter had no effect upon the hourly production of heat (unpublished). In this individual the reduction of body temperature was therefore wholly dependent on the mechanism of the physical regulation of temperature.

On the whole, these experiments show that in fever the increase in metabolism and of body temperature occur simultaneously. Further experiments planned along these lines, using other fevers and perhaps even shorter periods, will, it is hoped, give clearer evidence whether there is any reason for an increased heat production other than a rise in body temperature; or whether there is usually a preliminary stimulus to increased metabolism before the rise in body temperature occurs.

Nebelthau has shown a fall in temperature and heat production in a rabbit whose cord was divided between the sixth and seventh cervical vertebræ, and has also demonstrated that under these circumstances infection with erysipelas of the pig had no influence on temperature or heat production. The inference is that the febrile toxins act through the higher vasomotor centers, whose regulatory control is lost in the above experiment.

A kindred interpretation may be placed on the experiments of Mendelson,[1] who was unable to produce fever through pus injections when the dog was under the influence of chloral or

[1] Mendelson: "Virchow's Archiv," 1885, c, 274.

morphin, although such treatment in a normal animal caused a rise in temperature of from 36.3° to 39.9° in forty-five minutes. Mendelson also finds a constant constriction of the renal blood-vessels in fever.

Further experimentation convinced Sawadowski[1] that fever cannot be produced after the mid-brain has been severed from the medulla, whereas if the mid-brain be left intact, but the cerebrum be sectioned from it, fever may be induced in the ordinary course. Citron and Leschke[2] have found that destruction of the median portion of the 'tween brain on the boundary between the optic thalamus and the corpus quadrigeminum anterius, the "'tween brain puncture," converts a rabbit into the equivalent of a cold-blooded animal. Under these circumstances it is impossible to produce infective or non-infective fevers of any kind. The toxic substance must therefore act on nerve-cells in the mid-brain, which, in turn, stimulate the medullary centers.

At times during high fever the skin may be red and the peripheral blood-vessels distended. Although there is no sufficient explanation for the continuance of fever when the radiation and conduction of heat from the surface of the body are thus increased, Krehl[3] suggests that the quantity of blood flowing through the vessels at the time may be inadequate to reduce the body's temperature.

The second means of physical regulation of the body temperature is through the evaporation of water from both the lungs and the sweat-glands. It might be surmised that the activity of this mechanism was reduced in fever. Nebelthau[4] has shown that the heat lost by evaporation of water and by radiation and conduction bear exactly the same ratio to each other in normal and in fever-infected rabbits. Since Rubner (p. 140) has proved that the elimination of water in normal

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[1] Sawadowsky: "Centralblatt für medizinische Wissenschaft," 1888, xxvi, 161.

[2] Citron and Leschke: "Zeitschrift für ex. Path. und Ther.," 1913, xiv, 379.

[3] Krehl: "Pathologische Physiologie," 1904, p. 453.

[4] Nebelthau: *Loc. cit.*

animals greatly increases at high temperatures, the mere maintenance of the usual water evaporation during fever would of itself be abnormal.

Lang[1] has shown that the elimination of sweat is reduced during the rise of temperature in man, but at the height of fever is the same as the normal, while there is some increased evaporation from the lungs. He has also shown that the secretion of sweat is increased 50 per cent. after the ingestion of food as against an increase of 70 per cent. in the normal individual.

Recent experiments by Schwenkenbecker and Inagaki[2] show that the "insensible perspiration" in fever is as great as in health, and that although the urine may decrease in quantity there is no actual accumulation of water in the body as was believed by von Leyden (see p. 522).

Calculations made by Soderstrom[3] from the work of Coleman and DuBois show that in typhoid fever, when the body temperature is rising, the heat lost by water vaporization through the skin and lungs bears a lesser relation to the total heat elimination than occurs in normal individuals. On the contrary, a fall in body temperature is accompanied by a relative increase in the water elimination. These experiments confirm the ideas of von Leyden,[4] which were published in 1868.

The production of heat in fever may be greatly increased during a chill, and a rapid rise in temperature may follow. This was shown by Liebermeister[5] in a case of malaria. The temperature rose from 36.9° in the first half-hour to 39.5° at the end of another hour, while the carbon dioxid expired rose from 14.85 grams to 34.20 grams per half-hour. Barr, Cecil, and Du Bois (unpublished experiments of 1917) have found that during the chill in malaria or the chill following intravenous

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[1] Lang: "Deutsches Archiv für klinische Medizin," 1904, lxxix, 343.

[2] Schwenkenbecker and Inagaki: "Archiv für ex. Path. und Pharm.," 1906, liv, 168.

[3] Soderstrom: Unpublished

[4] von Leyden: "Deutsches Archiv für klinische Medizin," 1869, v, 273.

[5] Liebermeister: *Ibid.*, 1871, viii, 153.

injection of typhoid vaccine the extra heat produced was retained in the body, causing the sudden rise in body temperature. The amount and manner of heat loss was essentially unchanged from level of the previous normal, suggesting that the heat retention was due to a failure of the vasodilator system to respond normally. The chill ensued even when a patient was surrounded with hot-water-bags at a temperature of 42° C., indicating that the phenomenon was not due to the mechanism of chemical regulation as held by Krehl.[1]

Infectious fevers are characterized by a toxic destruction of body protein. Sometimes, as in the earlier stages of tuberculosis, this tissue destruction may be present in the absence of fever itself. Such a toxic action on body protein is also observed in cancerous cases, as was described by Fr. Müller.[2] He writes: "In the 7 cases (of carcinoma) cited, the nitrogen excretion was larger than the nitrogen ingestion, and consequently the body lost protein. In 2 cases the protein loss was no greater than in healthy individuals with similar insufficient nourishment. In all the other cases the protein metabolism was decidedly above that of healthy men under the same conditions. Even an ample dietary was not able to establish nitrogen equilibrium. As more food was given the nitrogen elimination rose higher and higher, but the point of nitrogen equilibrium seemed unattainable." Müller compared the cachexia of carcinoma with that found in febrile processes and believed them to be analogous.

Under these conditions the heat production may be increased 30 or 40 per cent. above the normal, despite the characteristic cachexia.[3] In milder cases of carcinoma, however, an increase in metabolism is not apparent.[4]

As regards tuberculosis May[5] writes: "Larger quantities of the toxins produce, with certain exceptions, a direct injury to

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[1] Krehl: "Pathologische Physiologie," 1904, p. 452.
[2] Müller, F.: "Zeitschrift für klinische Medizin," 1889, xvi, 496.
[3] Wallersteiner: "Deutsches Archiv für klinische Medizin," 1914, cxvi, 145.
[4] Magnus-Levy: "Zeitschrift für klinische Medizin," 1906, lx, 177.
[5] May: Ott's "Chemische Pathologie der Tuberculose," Berlin, 1903, p. 335.

the cell protoplasm. They are strongly toxic. The quantity of protein destruction attributable to this cause is not very large and becomes of importance only when continued for a long period of time and where there is no compensatory regeneration. It appears that the power to regenerate on the part of these cells which are destroyed by toxins is greatly reduced and in severe cases entirely lost."

Other fevers show a high toxic destruction of protein. F. Müller[1] reports a daily loss of 10.8 grams of nitrogen (equal to 318 grams of muscle) by a typhoid patient during eight days of fever when the daily food contained 8.3 grams of protein nitrogen and about 1000 calories. Administration of antipyrin which lowered the body temperature somewhat lessened the protein destruction. During fever in croupous pneumonia the protein metabolism is much higher than normal. After the crisis there is still a large excretion of nitrogen in the urine which continues until the croupous exudate has been decomposed by autolysis, absorbed by the blood, and metabolized in the body (epicritical nitrogen elimination). In acute pneumonic phthisis (galloping consumption), with its caseous transformation of lung tissue, there is a very high waste of tissue protein. F. Müller[2] has shown that while the croupous exudate readily undergoes autolysis at a temperature of 40°, with the production of deutero-albumoses, lysin, leucin, tyrosin, etc., the caseous mass does not undergo autolysis, although it permits free diffusion of soluble material, such as phosphates. Hence, although the protein of the cheesy mass is insoluble in the organism, the soluble toxins may be absorbed from the diseased part, and be the causative agent of the rapid destruction of body protein in galloping consumption.

The toxic destruction of protein in infective fever was definitely established by Kocher,[3] who found that after giving to a typhoid patient a diet containing carbohydrate in large

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[1] Müller, F.: "Centralblatt für klinische Medizin," 1884, v, 569.

[2] Müller, F.: "Verhandlungen des 20ten Congresses für innere Medizin," 1902, section iv, p. 192.

[3] Kocher: "Deutsches Archiv für klinische Medizin," 1914, cxv, 106.

amount and containing very little protein it was absolutely impossible during the febrile period to reduce the output of urinary nitrogen to that corresponding to the low level of the normal "wear and tear" quota of protein metabolism. With the decrease in the intensity of the febrile process the loss of body nitrogen gradually diminished. This appears in the following table:

PROTEIN METABOLISM IN TYPHOID FEVER

Weight, 57.5 to 59.8 kgm.

Day of Fever.	Food.			N in Excreta.	N Loss.	Uric Acid, Gm.	Highest Temp.
	Cal.	N.	Cal. per Kg.				
10	3448	4.7	60	21.09	−16.39	1.38	39.2°
11	3335	4.7	58	18.35	−13.75	1.26	39.3°
12	3213	2.2	56	.....	.....	.....	39.3°
13	3213	2.2	56	16.9	−14.7	0.93	38.75°
14	3213	2.2	56	16.46	−14.26	1.23	38.7°
15	3213	2.2	56	15.4	−13.2	1.01	38.45°
16	3213	2.2	56	10.4	−8.2	0.68	37.3°
17	3213	2.2	56	5.76	−3.56	0.58	37.6°
18	4666	3.5	78	6.70	−3.20	0.61	38.1°
19	4666	3.5	78	6.79	−3.29	0.45	37.1°
20	4666	3.5	78	5.81	−2.31	0.41	Normal.
21	4666	3.5	78	5.93	−2.43	0.26	Normal.

Daily creatinin reduced from 2.5 to 1.5 grams.

Although the nitrogen in the urine of a normal man when this diet is given ranges between 2.5 to 4 grams, during the febrile period of this typhoid patient it averaged 16 grams and even reached 20 grams per day. Creatinin, uric acid, sulphur, and phosphorus elimination were increased during the febrile period, but declined with the decline in protein metabolism.

Coleman and DuBois[1] gave to typhoid patients diets which contained much larger quantities of protein (as much as 16 grams of nitrogen daily), but they were unable to obtain nitrogen equilibrium, even though the diet was rich in carbohydrate. The following table gives a summary of their data:

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[1] Coleman and DuBois: "Archives of Internal Medicine," 1915, xv, 887.

CHART SHOWING NEGATIVE NITROGEN BALANCES IN TYPHOID PATIENTS WHO RECEIVE FOOD CALORIES IN EXCESS OF CALCULATED HEAT PRODUCTION. RESULTS ARE AVERAGES PER DAY

Patient.	Dates or Days of Disease, Inclusive.	Days in Period.	Range of Maximum Temperature, Degrees F.	Calculated Heat Production, Cal.	Food Calories.	Food N, Gm.	Nitrogen Balance, Gm.
Morris S..	Oct. 23–Nov. 3	12	102.8–104.6	2266	2863	16.4	−4.4
	Dec. 19–24	6	101.9–105.1	2085	2989	13.2	−2.4
Charles F.	Nov. 28–30	3	101.2–103.4	1752	2458	12.0	−4.6
Karl S....	Jan. 12–18	7	101.0–105.0	2197	2985	16.1	−3.2
	Jan. 19–22	4	98.8– 99.0	1678	2819	14.6	−1.9
John K...	Jan. 15–20	6	103.2–104.0	2568			
	Days of Disease.						
Frank W.	11–14	4	104.0–105.4	2200	2250	11.3	−5.0
	15–19	5	103.0–104.0	2238	3320	15.3	−3.3
	20–23	4	101.0–103.6	2054	2362	15.9	−1.5

Coleman and DuBois conclude that, though there was ample protein in the diet to establish nitrogen equilibrium in the normal man, it could not accomplish this in typhoid fever. It was impossible to escape the conclusion that the destruction of protein is caused by the toxins of the disease. In some cases the protein destruction continued several days after the body temperature had reached a low level.

In all fevers the septic products act upon the hunger centers in the brain, and appetite is wanting. This is evidenced throughout the course of tuberculosis, for example, and tends in this case to weaken the body's resistance through undernutrition. Forced feeding is therefore resorted to.

The experiments of von Hösslin[1] strongly affirmed the beneficence of a liberal diet in ordinary fevers. He writes: "The results show that febrile patients, or at least those who do not run temperatures above 40° to 40.5°, can digest and absorb the total amount of protein, fat, and carbohydrates which can be given them with their diminished appetite, provided the

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[1] von Hösslin: "Virchow's Archiv," 1882, lxxxix, 317.

food is administered in a proper form. Temperature and metabolism are only slightly increased thereby."

The efficiency of a carbohydrate diet in typhoid fever was first demonstrated by Shaffer and Coleman,[1] who showed that the ingestion of large amounts of carbohydrate in a medium protein diet may almost maintain the patient in nitrogen equilibrium throughout the disease. The diet consisted of milk, milk-sugar, diluted cream, eggs, and sometimes arrowroot starch. Shaffer writes: "It was only when we gave 60, 70, or even 80 calories per kilogram of body weight—between 3000 and 4000 calories—that the greatest sparing was observed."

The results obtained from two individuals suffering from typhoid are presented in the following table:

INFLUENCE OF CARBOHYDRATES ON PROTEIN METABOLISM IN TYPHOID FEVER

Subject I.

Period.	No. of Days in Period.	Range of Maximum Temp. During Period.	Total Calories of Food.	Calories per Kg.		Nitrogen in Food.	Nitrogen to Body.
				Total.	From carbohydrates.		
I.	4	104 –103.2° F.	4280	72	48.0	13.9	− 0.9
II.	6	103.6–102.8° F.	5200	85	48.0	15.0	− 0.2
III.	4	103.8–103.4° F.	2750	45	7.0	15.0	− 8.5
IV.	8	104.8–101.4° F.	5340	89	52.0	14.5	− 2.8
V.	6	100.8–99.4° F.	4990	83	48.0	13.8	+ 1.2
VI.	4	Normal.	2430	41	7.0	13.5	− 0.3

Subject II.

I.	9	104.4–102.6° F.	1920	31	7.8	12.6	−11.3
II.	6	102.8–100.6° F.	4290	70	47.0	12.6	*− 1.1
III.	6	Normal.	1930	32	8.0	12.7	− 3.8
IV.	8	102.8–99.6° F. Relapse.	4800	78	50.0	14.1	+ 3.6
V.	6	Normal convalescence.	2460	39	12.0	14.6	+ 1.8

* Average for last three days of diet.

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[1] Shaffer: "Journal of the American Medical Association," 1908, li, 974; Shaffer and Coleman, "Archives of Internal Medicine," 1909, iv, 538.

From this it may be concluded that nitrogen equilibrium may be very nearly maintained throughout the course of typhoid fever on a diet containing 12 to 15 grams of nitrogen, provided an excess of carbohydrate beyond the requirement of the organism be also administered. Very likely under these circumstances the fat in the diet is without influence, except that it is retained in the organism. Upon this basis rests the very notable advance achieved by the Coleman-Shaffer "high calorie diet."

Pioneer work with accurate technic upon the subject of the respiratory metabolism in typhoid fever was first accomplished by Kraus,[1] Grafe,[2] Rolly,[3] and Coleman and DuBois,[4] but the most complete work upon the subject is presented in the calorimeter studies of Coleman and DuBois which have already been incidentally alluded to. These authors give the following table which shows the correspondence between direct and indirect calorimetry obtained with patients suffering from typhoid:

	INDIRECT.	DIRECT.	DIVERGENCE.
			Per cent.
Total calories measured in all experiments	12,822.03	12,539.67	−2.2
Excluding first periods	8,470.93	8,488.97	+0.2
Calories measured in febrile experiments excluding all first periods	5,720.21	5,583.55	−2.4

Ten individuals were investigated. Metabolism records were obtained on sixty-five days. Twenty-four of these were devoted to the study of Morris S., a patient whose metabolism was determined through the course of the fever and two relapses, and one year later when he returned to the hospital in perfectly normal health. This gave the opportunity of

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[1] Kraus: "Zeitschrift für klin. Med.," 1891, xviii, 160.
[2] Grafe: "Deutsches Archiv für klin. Med.," 1911, ci, 209.
[3] Rolly: *Ibid.*, 1911, ciii, 93.
[4] Coleman and DuBois: "Archives of Internal Medicine," 1914, xiv, 168.

contrasting the effect of the specific dynamic action of protein in the same individual in fever and in health.

Coleman and DuBois state that the average increase in the basal metabolism in typhoid fever is approximately 40 per cent., although figures of over 50 per cent. are frequently encountered. The following table shows the average results obtained during the various weeks of typhoid fever:

BASAL METABOLISM, ACCORDING TO PERIODS OF TYPHOID FEVER

Periods.	Number of Patients.	Number of Observations.	Average Per Cent. Rise Above Average Normal 34.7 Calories per Sq. M.	Average Respiratory Quotient.
Ascending temperature...	2	2	+37	0.79
Continued temperature....	5	7	+42	0.77
Early steep curve..........	3	4	+26	0.82
Late steep curve..........	3	3	+16	0.82
Relapse—				
Ascending temperature..	2	3	+25	0.82
Continued temperature..	2	2	+51	0.76
Early steep curve.......	2	4	+36	0.78
Late steep curve........	1	1	+16	0.79
Convalescence—				
First week.............	3	4	− 2	0.91
Second week...........	3	5	+ 6	0.88
Third week............	1	1	+17	0.81
Fourth week...........	2	2	+15	0.86
Fifth week.............	2	2	+ 4	0.81

The considerable increase in metabolism during the second, third, and fourth weeks of convalescence is a noteworthy discovery. It is during this period that a regeneration of body protein takes place, and DuBois points out that the heightened metabolism is reminiscent of the increased heat production during the period of growth.

The specific dynamic action of food administered in typhoid fever was found to be almost negligible, although during convalescence it was as high as in normal individuals. The following table shows these results:

SPECIFIC DYNAMIC ACTION OF PROTEIN AND CARBOHYDRATE IN HEALTH, FEVER, AND CONVALESCENCE

Subjects.	Number of Experiments.	Average Gm. of Nitrogen or Glucose in Food.	Average Gm. Food per Kg. Body Weight Nitrogen or Glucose.	Average Per Cent. Rise in Metabolism.
Protein meal.				
Two normal men*.....	2	10.1	0.147	9.3
Four febrile patients...	6	8.6	0.174	4.5
Four convalescents....	5	10.2	0.217	16.6
Commercial glucose.				
Three normal men*....	3	115.0	1.6	9.1
Two febrile patients...	4	115.0	2.2	1.0
Three convalescents....	3	115.0	2.7	9.8

* Since the completion of Paper 4 two more normal controls have been given the test-meals. Morris S., on Dec. 18, 1914, showed a rise of 6.5 per cent. after a meal containing 9.6 gm. N.; Albert G., on Jan. 6, 1915, showed an increase of 9 per cent. in his metabolism after 115 gm. commercial glucose.

The meal containing protein was as large as the patient could be persuaded to take. The results of the ingestion of large amounts of food caused only a slight increase in the basal metabolism during fever, one of 5 per cent. in the case of protein and only 1 per cent. in the case of commercial glucose. The ancient doctrine of "starving a fever" herewith falls to the ground.

The effect of bodily activity upon the basal metabolism does not appear to be as marked during typhoid fever as in health. Thus, Coleman and DuBois describe how Morris S. was quiet during a first hour, was restless and tossed about the bed during a second hour, and during a third hour was evidently irrational, tossed about, wrote several long notes which he held up to the calorimeter window, telling of animals that were biting him with their sharp teeth. Yet his metabolism, which was 43 per cent. above the normal for the three-hour period, was only 5 per cent. higher than during a quiet period of observation of the basal metabolism made two days later when the body temperature was lower.

The principal cause of the increased metabolism in typhoid fever lies, therefore, in the febrile process itself, and food and restlessness have little influence.

The respiratory quotients were normal, the lowest being 0.72, obtained during fasting, and the highest 1.04, obtained after carbohydrate ingestion.

The large quantities of food administered to the typhoid patients in the "high calorie diet" are as completely absorbed as they would be in health.[1]

Only a résumé of the more important principles involved can be attempted in this book, and those interested in the metabolism of typhoid patients are referred to the details in the original communication of Coleman and DuBois.

An illustration of the course of nitrogen metabolism in a different fever—namely, pneumonia—may also be taken from von Leyden and Klemperer.[2] The details are given below:

METABOLISM IN PNEUMONIA

Temp. on Successive Days.	Food.					Excreta.			Loss of Body N.
	Quantity in Grams.	Calories.	N.	Fat.	Carbohydrates.	Urine N.	Feces N.	Total N.	
40.8 (highest).	2000 milk.	1360	10.6	70	90	24.7	0.9	25.6	15.0
40.9 (highest).	2000 milk, 150 cream, 100 lactose.	1980	11.4	85	197	22.8	0.9	23.7	12.3
41.2 at 12 M. 36.8 at 7 P. M.	2000 milk. 150 lactose.	1975	10.6	70	240	21.7	0.9	22.6	12.0
37.3 (highest).	2000 milk, 200 cream.	1612	11.7	90	99	21.9	1.1	23.0	11.3
36.8 (highest).	2000 milk, 200 cream, 2 eggs.	1752	13.7	100	99	18.5	1.1	19.6	5.9
36.8 (highest).	2000 milk, 300 cream, 4 eggs.	2018	17.3	120	104	18.7	1.1	19.8	2.5

In this case it is apparently demonstrated that nitrogen equilibrium cannot be obtained during high fever, and also that the loss of body nitrogen does not cease at the crisis, but

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[1] DuBois: "Archives of Internal Medicine," 1912, x, 177; Coleman and Gephart: *Ibid.*, 1915, xv, 882.

[2] von Leyden and Klemperer: "Handbuch der Ernährungstherapie," 1904, Bd. ii, p. 345.

rather continues on account of the epicritical elimination of nitrogen derived from the protein of the croupous exudate. During the time of this epicritical elimination the body appears unable to add new protein to itself. About four days after the crisis true convalescence begins, with the upbuilding of new protein tissue.

On autopsy of patients who have died of fevers, parenchymatous and fatty degenerations of the organs have been found. These changes have been ascribed to overheating of the cells.

Litten[1] warmed guinea-pigs artificially and noted fatty but no parenchymatous degeneration of the tissues. The space in which the animals were kept was, however, insufficiently ventilated, and the fatty change might have been caused by dyspnea, as results in normal animals (p. 423).

Naunyn[2] observed that rabbits might be artificially warmed for thirteen days, so that an average body temperature of 41.5° was maintained without any parenchymatous or fatty degeneration taking place. The animals were supplied with ample food, water, and a sufficient supply of air. Naunyn found that the red blood-cells of rabbits and dogs remained intact even at a body temperature of 42°. Welch[3] noticed fatty but no parenchymatous change in the tissues of rabbits after exposure to high temperature for at least a week. One rabbit which had been subjected to high temperature for four days was inoculated with the bacilli of the swine plague and died in thirty-six hours, showing extreme fatty changes in the heart and other organs.

Ziegler[4] discovered degenerative changes, both parenchymatous and fatty, on artificially warming rabbits. The experiment was continued in 1 case for twenty-nine days. He found, however, a great reduction (30 per cent. and more) in the quantity of hemoglobin in his rabbits. It may well be a question whether the fatty change noticed in the liver and

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[1] Litten: "Virchow's Archiv," 1877, lxx, 10.
[2] Naunyn: "Archiv für ex. Path. und Pharm.," 1884, xviii, 49.
[3] Welch: "Medical News," 1888, lii, 403.
[4] Ziegler: "Kongress für innere Medizin," 1895, xiii, 345.

muscles was not due to anemia instead of to the hyperthermia. Since fatty infiltration is known to be caused by dyspnea, which frequently terminates life in fever, one might investigate this subject to see whether parenchymatous change in fever is not solely due to the toxins, and fatty change to the anaërobic cleavage of materials in the cells, which always induces fatty infiltration (p. 489).

Rosenthal[1] states that if diphtheria toxin be administered to rabbits the liver is rendered incapable of retaining glycogen. There is hypoglycemia except following glucose administration, when a hyperglycemia greater than that possible in normal animals occurs.

Ever since the experiments of von Leyden[2] a retention of water in fever has been assumed. It has also been shown that there is a retention of sodium chlorid within the body. The intimate relation between the retention of water and salt has been beautifully demonstrated by Sandelowsky[3] in Lüthje's clinic. Thus, during the period of high fever in pneumonia a gain in weight, a sodium chlorid retention, and a dilution of the organic contents of the blood usually went hand in hand. After the crisis, however, a loss in weight, a loss of chlorid, and a greater concentration of blood resulted. Similar conditions were found in scarlet fever.[4] Sandelowsky observed that when sodium chlorid was given to a patient convalescent from pneumonia it was not so readily eliminated by the kidney as it would have been normally. He attributed this to a disturbed renal condition which was not wholly restored to the normal after the crisis. This brought about sodium chlorid retention, which in turn caused water retention, that the normal osmotic conditions might be preserved, thus accounting for the gain in body weight and the loss in the concentration of the blood in fever.

It has since been shown that failure to excrete chlorid

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[1] Rosenthal, F.: "Archiv für ex. Path. und Pharm.," 1914, lxxv, 99.

[2] von Leyden: "Deutsches Archiv für klin. Med.," 1869, v, 273.

[3] Sandelowsky: *Ibid.*, 1909, xcvi, 445.

[4] Oppenheimer and Reiss: *Ibid.*, p. 464.

during the acute stage of the disease is almost always associated with a concentration of sodium chlorid in the blood-plasma below 5.62 grams per liter, which is the normal threshhold value of excretion[1] (see p. 167). Hence the retention of sodium chlorid is not due to kidney insufficiency.

As regards the etiology of fever, various attempts have been made to identify a single factor which would cause the high temperature.

Krehl and Matthes[2] find that human urine during fever contains an increased quantity of albumoses which have been shown to possess a decidedly toxic action when introduced into animals. Klemperer[3] denies that these albumoses have any toxic action, and asserts that the results were due to impurities in preparation. In other respects the urine has generally been found to be of normal character. Thus, Mohr[4] finds that the relation C to N in the urine is unchanged from the normal, which indicates that there is no qualitative change in the character of the general protein metabolism

However, there is a very noteworthy record made by A. R. Mandel[5] that the rise of temperature in so-called aseptic or surgical fevers is accompanied by a large increase in the purin bases in the urine of patients fed with milk. The temperature rises and falls with the quantity of purin bases eliminated. The uric acid elimination is reduced. These relations are illustrated in Fig. 27—a case of resection of the knee-joint for tubercular arthritis. The temperatures recorded represent the average of observations made every three hours during the day.

Another research available in this connection is that of von Jaksch,[6] who noted that the purin bodies in the urine of

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[1] Snapper: "Deutsches Archiv für klin. Med.," 1913, cxi, 429; McLean, "Journal of Experimental Medicine," 1915, xxii, 366.

[2] Krehl and Matthes: "Deutsches Archiv für klinische Medizin," 1895, liv, 501.

[3] Klemperer: "Naturforscherversammlung," 1903, 2, ii, 67.

[4] Mohr: "Zeitschrift für klinische Medizin," 1904, lii, 371.

[5] Mandel: "American Journal of Physiology," 1904, x, 452.

[6] von Jaksch: "Zeitschrift für klinische Medizin," 1902, xlvii, 1.

tuberculous patients may increase from a normal equivalent of 4.4 per cent. of the total nitrogen excreted, to one representing 11.3, or even 17.39 per cent. Also Benjamin[1] reports a case of typhoid where the urine contained the large quantity of 0.1 gram of purin bases with 0.54 gram of uric acid. Erben[2] and Leathes[3] report that the output of uric acid is always increased during high fever. Erben also finds that the content of the urine in xanthin bases and amino-acids is greatly augmented in measles and chicken-pox; and that the xanthin bases are also increased, though to a lesser extent, in scarlet fever and typhoid. Mandel[4] has fed monkeys with bananas and xanthin and witnessed a rise in body temperature, and has noticed that if sodium salicylate be given at the same time no

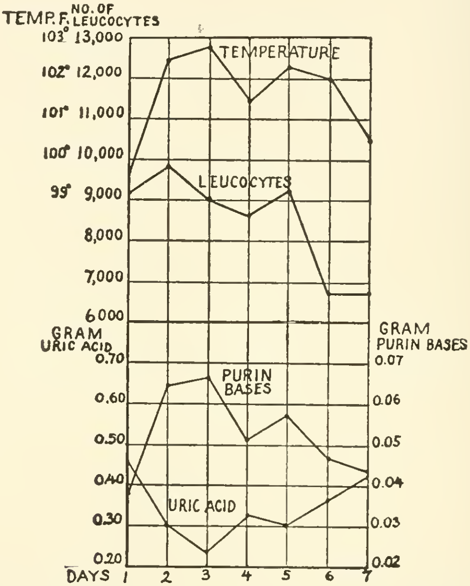

Fig. 27.—Resection of knee-joint for tubercular arthritis.

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[1] Benjamin: "Salkowski's Festschrift," 1904, p. 61.

[2] Erben: "Zeitschrift für Heilkunde," 1904, xxv, 33.

[3] Leathes: "Journal of Physiology," 1907, xxxv, 205.

[4] Mandel: "American Journal of Physiology," 1907, xx, 439.

rise in temperature occurs. Ott[1] reports that guanin, adenin, and hypoxanthin cause an elevation of temperature in rabbits, while uric acid does not.

Mandel believes that the purin bases liberated through the toxic destruction of tissue may play a considerable part in producing the temperatures noted in fever. It is evident that the use of purin-free milk instead of purin-containing meat has its scientific justification.

It would indeed be a most striking fact if it should be found that the cause of the febrile temperature lies in the effect of purin bases on the heat-regulating apparatus of the mid-brain acting through the vasomotor system. Antipyretics do not lower body temperature in the normal organism in man. Is their action merely to nullify the action of purin bases upon the nerve-centers? Future research alone can decide this. Such conjectures indicate the extraordinary field which lies open to the investigator in clinical medicine.

[1] Ott: "The Medical Bulletin" (Medico-Chir. College), October, 1907.

CHAPTER XIX

PURIN METABOLISM—GOUT

URIC acid was discovered in urinary calculi by Scheele in 1776, and was found to be present in gouty concretions by Wollaston in 1797. It has since been the subject of investigations almost without number, and of theoretic speculation beyond that of any other chemical substance described in medical literature. The older work concerning the excretion of uric acid is almost valueless on account of the inadequacy of the chemical methods of the times. Accurate determinations of uric acid date from the introduction of a new method of analysis by Salkowski in 1882; and of allantoin by Wiechowski in 1908.

The newer researches are also based on more exact chemical knowledge of the precursors of uric acid. Much valuable information has been gathered as regards the normal method of production of uric acid, although it will be seen that on the pathologic side there is little beyond the conjectural to reward the student.

Emil Fischer[1] grouped together uric acid, hypoxanthin, xanthin, adenin, and guanin as bodies whose varying structure depended upon slight changes around the chemical nucleus of a substance called purin. Purin, according to Fischer, may occur in the body, but on account of its ready decomposability, has not been discovered there.

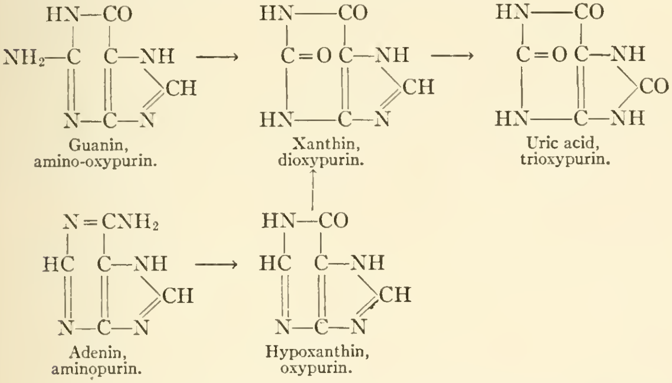
The relations between the purin bodies may be judged from the following formulæ:

Purin	$C_5H_4N_4$
Hypoxanthin	$C_5H_4N_4O$
Xanthin	$C_5H_4N_4O_2$
Uric acid	$C_5H_4N_4O_3$
Adenin	$C_5H_3N_4NH_2$
Guanin	$C_5H_3N_4ONH_2$

[1] Fischer: "Berichte der deutschen chemischen Gesellschaft," 1899, xxxii, 435.

Hypoxanthin, xanthin, and uric acid are respectively mono-, di-, and tri-oxypurin. Adenin is aminopurin, and guanin is aminohypoxanthin. It is evident that uric acid is the most highly oxidized product of the series, and might readily arise from the oxidation of hypoxanthin and xanthin. It is also apparent that by supplanting the NH_2 group in adenin and guanin by O, they would be converted into hypoxanthin and xanthin respectively, and that from these substances uric acid might arise through oxidation.

These reactions may be thus expressed:



Guanin, amino-oxypurin.

Xanthin, dioxypurin.

Uric acid, trioxypurin.

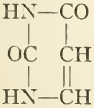
Adenin, aminopurin.

Hypoxanthin, oxypurin.

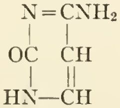
The deamination of guanin and adenin is accomplished by hydrolysis and may occur in the absence of oxygen, whereas the conversion of hypoxanthin into xanthin and the latter into uric acid are true processes of oxidation.

The knowledge of the hydrolytic cleavage products of nucleic acid is derived largely from the work of Kossel,[1] who added adenin, cytosin, and thymin to chemical literature.

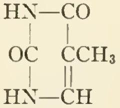
The formulæ of the three pyrimidin bases—uracil, cytosin, and thymin—are as follows:



Uracil.



Cytosin.



Thymin.

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[1] For the extensive literature on this subject consult the valuable monograph of Walter Jones, "Nucleic Acids," London, 1914.

Kossel and Steudel[1] point out the fact that purin bases contain the pyrimidin nucleus, and that cytosin, for example, needs only cyanic acid, CONH, and an atom of oxygen to convert it into uric acid.

They query whether the pyrimidin bases are precursors or metabolized products of the purins, but the question is still unsettled.[2]

Mendel and Myers[3] report that the pyrimidin bases, when administered intravenously or *per os*, reappear in the urine unchanged without increasing either the purin or the urea output. However, when nucleic acids containing pyrimidin bases are administered, the bases are not found in the urine. The pathway of their disintegration is uncertain.

Kossel's work presents the following substances as characteristic cleavage products of animal and vegetable nucleic acids:

ANIMAL.	VEGETABLE.
Thymus nucleic acid:	*Yeast nucleic acid:*
Phosphoric acid	Phosphoric acid
Guanin	Guanin
Adenin	Adenin
Cytosin	Cytosin
Thymin	Uracil
Hexose	Pentose

Bang[4] extracted from the pancreas a nucleic acid containing phosphoric acid, a pentose and guanin, which compound he called "guanylic acid." The presence of a pentose in animal nucleic acid is an anomaly. Levene and Jacobs[5] discovered the formula of guanylic acid, and solved the long-sought prob-

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[1] Kossel and Steudel: "Zeitschrift für physiologische Chemie," 1903, xxxviii, 49.

[2] Consult Abderhalden: "Lehrbuch der physiologischen Chemie," 1909, p. 381.

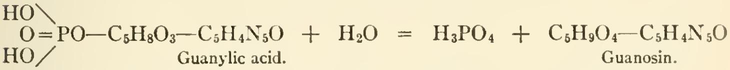
[3] Mendel and Myers, V. C.: "American Journal of Physiology," 1910, xxvi, 77.

[4] Bang: "Zeitschrift für physiologische Chemie," 1898–99, xxvi, 133.

[5] Levene and Jacobs: "Ber. d. d. chem. Ges.," 1909, xlii, 2469; "Journal of Biological Chemistry," 1912, xii, 421.

lem of the composition of nucleic acid. They submitted guanylic acid to neutral hydrolysis under pressure, which removed phosphoric acid and left a substance (guanosin) which readily broke up on acid hydrolysis into d-ribose and guanin.

These two hydrolyses may thus be written:

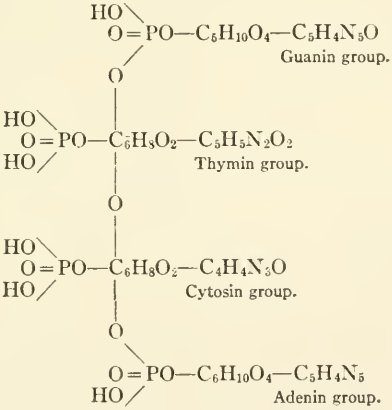


$$\underset{\text{Guanylic acid.}}{\begin{array}{l}HO\diagdown\\ \quad O{=}PO{-}C_5H_8O_3{-}C_5H_4N_5O\\ HO\diagup\end{array}} + H_2O = H_3PO_4 + \underset{\text{Guanosin.}}{C_5H_9O_4{-}C_5H_4N_5O}$$

$$\underset{\text{Guanosin.}}{C_5H_9O_4{-}C_5H_4N_5O} + H_2O = \underset{\text{d-Ribose.}}{C_5H_{10}O_5} + \underset{\text{Guanin.}}{C_5H_5N_5O}$$

Guanylic acid is a monobasic *nucleotid* which yields on cleavage phosphoric acid and the *nucleosid*, guanosin.

The more complicated nucleic acids are polymers of *nucleotids.* Thus, Levene and Jacobs[1] give the following formula for animal nucleic acid:



Levene and Medigreceanu[2] found that animal ferments have the power of hydrolytic cleavage over nucleic acid. Thus, pancreatic juice or intestinal juice through *nucleinase* (1) causes the resolution of a *polynucleotid* into *mononucleotids.* Animal tissues were also found to contain a similar ferment. Extracts of the mucosa of the intestine contained *nucleotidase*

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[1] Levene and Jacobs: "Journal of Biological Chemistry," 1912, xii, 411.

[2] Levene and Medigreceanu: *Ibid.*, 1911, ix, 389.

(2) which splits the nucleotids into phosphoric acid and *nucleosids.* The pyrimidin nucleosids are not further acted upon, but the purin nucleosids are broken up by *nucleosidase* (3) into their constituent carbohydrate and purin groups. The kidney, heart muscle, and liver contain all the above-named enzymes, and are, therefore, capable of demolishing the complex molecule of nucleic acid.

The enzyme nucleinase which breaks the polynucleotid complex of nucleic acid may not act as a simple unit. Thus, Jones and Richards[1] found that when the tetranucleotid, yeast nucleic acid, was mixed with pigs' pancreas it is split into two dinucleotids; one containing the guanin and cytosin groups, the other, the adenin and uracil groups. Not only this, but Thannhauser[2] found that after digesting yeast nucleic acid with human duodenal juice, the nucleotid containing uracil was split off and there remained a trinucleotid containing guanin, adenin, and cytosin. Various places of attack are therefore open.

Selecting the nucleotids forming yeast nucleic acid, one may present this summary of their transformation:

Nucleotids minus H_3PO_4	=	*Nucleosids* minus d-ribose	=	*Bases.*
Adenylic acid	⟶	Adenosin	⟶	Adenin
Guanylic acid	⟶	Guanosin	⟶	Guanin
Cytodin-nucleotid	⟶	Cytidin	⟶	Cytosin
Uridin-nucleotid	⟶	Uridin	⟶	Uracil

This is the simplest picture of the transformations which take place. Amberg and Jones[3] have shown that the deaminizing enzymes (see p. 531) may convert guanosin into *xanthosin,* which yields xanthin on hydrolysis, or convert adenosin into *inosin,* which yields hypoxanthin on hydrolysis.

Jones ("Nucleic Acids," p. 77) presents the following scheme of the methods of breakdown of a guanin-adenin dinucleotid:

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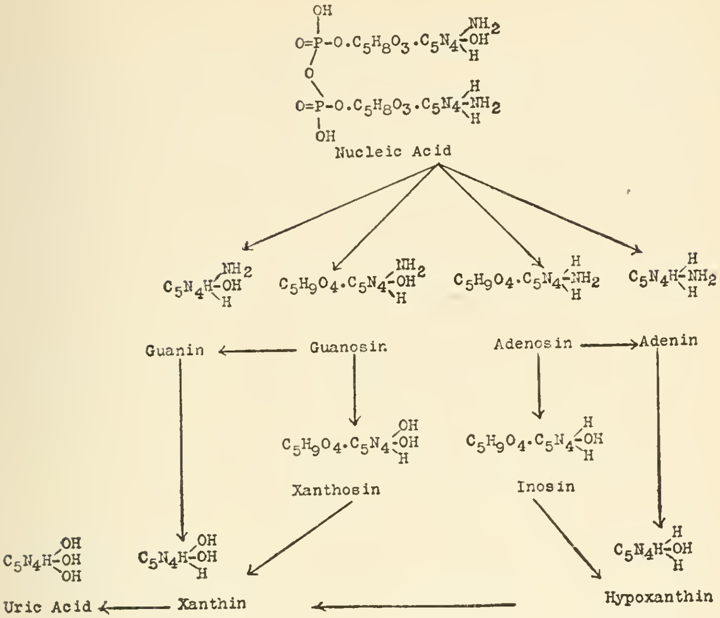
[1] Jones and Richards: "Journal of Biological Chemistry," 1914, xvii, 71.

[2] Thannhauser: "Zeitschrift für physiologische Chemie," 1914, xci, 329; 1915, xcv, 259.

[3] Amberg and Jones: *Ibid.*, 1911, lxxiii, 407.



Horbaczewski[1] was the first to note that the ingestion of nucleoproteins largely increased the uric acid in the urine. Food free from nucleoproteins has not this effect. He also found that if fresh spleen pulp, which contains no uncombined purin bases, be permitted to putrefy, xanthin and hypoxanthin made their appearance. If now the pulp was shaken in the air, uric acid was formed from the oxidation of the bases.

Spitzer[2] found that when air was passed through aqueous extracts of spleen and liver digested at 40°, and with exclusion of putrefaction, uric acid was produced. The quantity of purin bases present decreased with the increased formation of uric acid. Purin bases added to such a digest were converted into uric acid, hypoxanthin, and xanthin readily and almost completely, and guanin and adenin with greater difficulty. This work established the presence of oxidizing enzymes, the

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[1] Horbaczewski: "Sitzungsberichte der Wiener Academie der Wissenschaft," 1891, c, Abth. iii, p. 13.
[2] Spitzer: "Pflüger's Archiv," 1899, lxxvi, 192.

xanthin oxidases, which could act on the purin bases in the organism, converting them into uric acid.

Minkowski[1] has shown that if a man be given hypoxanthin the quantity of uric acid increases in his urine. He also showed that if a man ingest thymus gland, the nuclein of which yields principally adenin, the amount of uric acid is increased in the urine. If the thymus be given to a dog, the uric acid plus allantoin elimination is increased. Allantoin is an oxidation product of uric acid more frequently found in dogs' than in human urine. Minkowski discovered finally that adenin when administered to a dog did not increase the uric acid elimination, and was not excreted as such, but on autopsy of the dog the uriniferous tubules were found to contain crystals the chemical structure of which showed them to be aminodioxypurin. In other words, adenin administered combined in nucleic acid loses its amino (NH_2) group, receives three atoms of oxygen, and is thereby converted into uric acid; adenin administered as such receives two atoms of oxygen, but does not lose its NH_2 group at the point for the attachment of the third atom of oxygen. This work attests a varying behavior of purin bodies in accordance with their method of chemical union with other substances, and offers a suggestive key to certain relations observed in gout (p. 546).

When theophyllin, caffein, and theobromin, the methylated purins found in tea, coffee, and cocoa, are ingested it has been stated that they are not oxidized to uric acid, but that they increase the purin bases in the urine.[2] However, both Levinthal[3] and Stanley Benedict[4] have found the uric acid elimination to increase in man after the ingestion of 1 to 1.5 gram of caffein daily.

The original investigations of Horbaczewski have been considerably extended by Schittenhelm and notably by

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[1] Minkowski: "Archiv für ex. Path. und Pharm.," 1898, xli, 375.

[2] Krüger and Schmid: "Zeitschrift für physiologische Chemie," 1901, xxxii, 104.

[3] Levinthal: *Ibid.*, 1912, lxxvii, 259.

[4] Benedict, S. R.: "The Harvey Lectures," 1915-16.

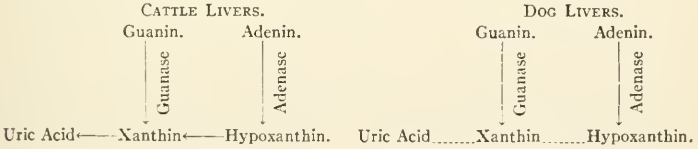
Walter Jones, especially in regard to their explanation along lines of enzymotic activity.

Jones and Partridge[1] find that although the great majority of the organs of the body, when self-digested at 40° (autolysis), convert guanin and adenin into xanthin and hypoxanthin, presumably through the action of enzymes, extracts of the spleen of the pig cannot convert guanin into xanthin, although they can convert adenin into hypoxanthin. Jones therefore concludes that an enzyme, guanase, which normally removes the NH_2 group and replaces it with O, is wanting in the pig's spleen, while adenase, the enzyme acting on adenin in a similar fashion, is present there. Such a reaction would read:

$$\underset{\text{Adenin.}}{C_5H_3N_4NH_2} + H_2O = \underset{\text{Hypoxanthin.}}{C_5H_5H_5O} + NH_3$$

Investigating the subject further, the authors found that the pancreas contained the enzyme, guanase, which converts guanin into xanthin.

The behavior of the livers of different animals has been investigated by Jones and Austrian.[2] In cattle livers, for example, adenase, guanase, and xanthin oxidase are present, whereas in dog livers guanase is present, adenase occurs in traces only, and no xanthin oxidase whatever has been found. Hence cattle livers may form uric acid from adenin and guanin, while dog livers only convert guanin into xanthin and the other processes are arrested. The process is thus graphically represented:



Cattle Livers.

Xanthin oxidase present.

Dog Livers.

Xanthin oxidase and adenase absent.

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[1] Jones and Partridge: "Zeitschrift für physiol. Chemie," 1904, xlii, 343; see also Levene, "American Journal of Physiology," 1904, xii, 276.

[2] Jones and Austrian: "Zeitschrift für physiologische Chemie," 1906, xlviii, 110.

Furthermore these authors find that the guanase is absent from pigs' livers, while adenase and xanthin oxidase are present. It is interesting that Mendel and Mitchell[1] have found in the liver of the embryo pig at an early age the same specific enzymes as characterize the liver of the adult animal. There was, however, a considerable delay in the appearance of the enzyme which oxidizes uric acid (see below). It is a curious phenomenon that pigs suffer from guanin gout. Their normal urines contain not only uric acid,[2] but also large amounts of purin bases.[3] The organs of the pig are deficient in guanase.[4]

Schittenhelm[5] reports that human livers have the power to form uric acid from added purins, and he believes that the power to oxidize uric acid exists.

Lauder Brunton[6] says that Stockvis, of Amsterdam, in 1860 found that crushed tissue had the power to destroy uric acid. This question has recently come into prominence and it has been shown that different organs have different powers in this regard, and that the same organ in animals of different species may behave quite differently.

Wiener[7] showed that dog's liver and pig's liver destroyed uric acid, whereas calf's liver had less power to do so, or none at all. The kidney pulp of various animals also destroyed uric acid.

Schittenhelm[8] finds that in cattle the spleen, lungs, liver, intestine, and kidney have the power of converting purin bases into uric acid in the presence of a constant oxygen supply. He finds a complete transformation of adenin, as follows: adenin, hypoxanthin, xanthin, uric acid. Guanin in like manner becomes xanthin and this again is converted into uric acid.

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[1] Mendel and Mitchell: "American Journal of Physiology," 1907, xx, 97.

[2] Schittenhelm and Bendix: "Zeitschrift für physiologische Chemie," 1906, xlviii, 140.

[3] Mendel and Lyman: "Journal of Biological Chemistry," 1910, viii, 115.

[4] Jones and Austrian: "Zeitschrift für physiologische Chemie," 1906, xlviii, 110.

[5] Künzel and Schittenhelm: "Zentralblatt für Stoffwechsel," 1908, iii, 721.

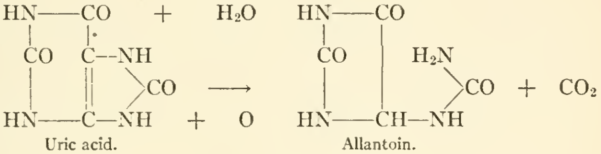
[6] Lauder Brunton: "Centralblatt für Physiologie," 1905, xix, 5.

[7] Wiener: "Archiv für exp. Path. und Pharm.," 1899, xlii, 375.

[8] Schittenhelm: "Zeitschrift für physiologische Chemie," 1905, xlv, 145.

He finds also that extracts of the spleen, intestines, and lungs have no power to destroy uric acid as formed within them, but that the kidney, muscle, and liver extracts possess the power to destroy the new-formed uric acid.

It is only recently that evidence has accumulated to show that the long believed physiologic oxidation of uric acid with the production of urea is impossible. To understand the subject it is necessary to consider the significance of allantoin which was first discovered by Wöhler in cows' urine in 1849. Salkowski[1] reported that the allantoin excretion increased in dogs after the administration of uric acid. The transformation of uric acid into allantoin takes place after the following reaction:



Cohn[2] gave large amounts of thymus to a dog and found that the excretion of allantoin was greatly increased, though this did not happen in man, and experiments by Minkowski,[3] performed during the same year, showed that when hypoxanthin was fed to a dog 77 per cent. of it appeared in the urine as allantoin, while 4 per cent. was eliminated as uric acid. Mendel and White[4] found that allantoin was eliminated in the urine of cats and dogs after the intravenous administration of urates.

It was long believed that allantoin was an intermediary product of the oxidation of uric acid. It is due to Wiechowski that the subject has become clarified. Wiechowski[5] found that uric acid digested with the pulp of dog's liver was oxidized completely to allantoin and no further, and also that uric

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[1] Salkowski: "Ber. d. d. chem. Ges.," 1876, ix, 719.
[2] Cohn: "Zeitschrift für physiologische Chemie," 1898, xxv, 507.
[3] Minkowski: "Archiv für exp. Path. und Pharm.," 1898, xli, 375.
[4] Mendel and White: "American Journal of Physiology," 1904–5, xii, 85.
[5] Wiechowski: "Hofmeister's Beiträge," 1907, ix, 295; 1908, xi, 109.

acid injected subcutaneously into a dog was almost completely eliminated as allantoin in the urine. These results were dependent upon the accurate method for the determination of allantoin which had been devised by the experimenter. It is evident, therefore, that the oxidizing enzyme uricase, which acts upon uric acid, carries its destructive power only as far as the production of allantoin, which is the end-product of purin oxidation.

An experiment[1] made many years ago demonstrated that if an Eck fistula, which excludes the portal blood from the liver, be created in a dog, uric acid appears in increased quantity in the urine. The interpretation long placed upon this was that in the absence of the liver uric acid was not oxidized. Repeating this experiment, Abderhalden, London, and Schittenhelm[2] found that the increase in uric acid elimination was compensated for by a decrease in allantoin excretion. The percentage values, contrasted with those in normal dogs' urine as established by Wiechowski, were as follows:

	Eck Fistula.	Normal.
Allantoin	74–87	94–97
Uric acid	12– 8	2– 4
Purin bases	1– 2	1– 2

It is evident that the liver is not the only organ in which uricase converts uric acid into allantoin.

Wiechowski found that the allantoin excretion of the cat followed the same laws as obtain in the dog, and Hunter and Givens[3] report that the extent and behavior of the allantoin excretion of the Wyoming coyote is practically identical with that of the dog.

Hunter and Givens[4] state that the excretion of purin bases in the monkey greatly exceeds the elimination of uric

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[1] Hahn, Massen, Nencki, and Pawlow: "Archiv für exp. Path. und Pharm.," 1893, xxxii, 191.

[2] Abderhalden, London, and Schittenhelm: "Zeitschrift für physiologische Chemie," 1909, lxi, 413.

[3] Hunter and Givens: "Journal of Biological Chemistry," 1910–11, viii, 449.

[4] Hunter and Givens: *Ibid.*, 1914, xvii, 37.

acid, a condition which also appears in the horse, sheep, pig, and goat. For the monkey the percentage figures are:

	Per Cent. Purin N.
Uric acid	7–8
Allantoin	67
Purin bases	25–26

When allantoin was given subcutaneously to the monkey 75 to 90 per cent. was recovered in the urine.

Hunter and Givens[1] present the following table showing the relative purin content in the urines of various species of animals:

Order and Species.	Per Cent. of Purin—Allantoin Nitrogen.		
	Allantoin.	Uric acid.	Bases.
Marsupialia:			
Oposum	76.0	19.0	6.0
Rodentia:			
Guinea-pig	91.0	6.0	3.0
Rat	93.7	3.7	2.7
Ungulata:			
Sheep	64.0	16.0	20.0
Goat	81.0	7.0	12.0
Cow	92.1	7.3	0.7
Horse	88.0	12.0	0.5
Pig	92.3	1.8	5.8
Carnivora:			
Raccoon	92.6	5.4	2.0
Badger	96.9	1.9	1.2
Dog	97.1	1.9	1.3
Coyote	95.6	2.6	1.8
Primates:			
Monkey	66.0	8.0	26.0
Man	2.0	90.0	8.0

An extraordinary exception to the rule of oxidation of uric acid to allantoin in the dog was discovered by Stanley Benedict[2] to be characteristic of the Dalmatian hound, or spotted coach dog. The urines of these dogs contain large amounts of uric acid. When uric acid is administered subcutaneously it is completely eliminated in the urine instead of

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[1] Hunter and Givens: "Journal of Biological Chemistry," 1914, xviii, 403.

[2] Benedict, S. R.: "The Harvey Lectures," 1915–16.

being oxidized to allantoin, as would happen ordinarily in the dog. This is a peculiar racial anomaly.

The urine of man is almost free from allantoin and the 10 to 15 milligrams which Wiechowski found therein may be accounted for as originating from traces of the substance found in common foods.[1]

Loewi[2] showed that the ingestion of the same amount of nucleoprotein-containing food by different people resulted in the excretion of the same increased quantity of uric acid in the urine, and he surmised that the uric acid which was produced in the human being was not oxidized. Confirmation of this idea was given by the discovery of Soetbeer and Ibrahim[3] that the subcutaneous injection of uric acid in man led to its complete elimination in the urine.

For a long time this viewpoint was overshadowed by experiments which showed only a moderate recovery of uric acid in the urine when purin bases in measured quantities were given to human beings. These results, which were interpreted to be due to the oxidation of the purins through the uric acid stage, are now attributed to their non-absorption or their putrefaction in the intestinal tract.

Wiechowski[4] found that allantoin injected subcutaneously is completely eliminated in human urine, which is normally free from it. He also found that human tissues have no power to oxidize uric acid; it can always be completely recovered. Therefore the human organism lacks the enzyme uricase.

In concordance with these results Umber and Retzlaff[5] find that if uric acid be dissolved in piperazin and be injected into a healthy human being, between 80 and 95 per cent. may be recovered in the urine; also Levinthal[6] injected 1 gram of

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[1] Ackroyd: "Biochemical Journal," 1911, v, 400.

[2] Loewi: "Archiv für exp. Path. und Pharm.," 1900, xliv, 1.

[3] Soetbeer and Ibrahim: "Zeitschrift für physiologische Chemie," 1902, xxxv, 1.

[4] Wiechowski: "Archiv für exp. Path. und Pharm.," 1909, lx, 185.

[5] Umber and Retzlaff: "Verhandlungen des 27ten Congresses für innere Medizin," 1910, Sec. III, p. 436.

[6] Levinthal: "Zeitschrift für physiologische Chemie," 1912, lxxvii, 259.

xanthin dissolved in piperazin into the vein of a healthy human subject, and concluded that, in all probability, all the xanthin which reached the metabolic circulation was completely eliminated without the rupture of the purin nucleus, the larger part being oxidized to uric acid and only a small remainder passing unchanged through the organism.

Finally, the experiments of Thannhauser and Bommes[1] deserve attention. When adenosin and guanosin were administered subcutaneously to normal men, between 75 and 82 per cent. of the purin bases contained in them were eliminated in the urine of the following twenty-four to forty-eight hours in the form of uric acid. These water-soluble purin-glucosids, adenosin and guanosin, are undoubtedly intermediary metabolites of nucleic acids.

The synthetic origin of purins in metabolism has been recognized since the work of Miescher (see p. 82). Kossel[2] showed that purins developed in the incubated egg, which when newly laid is free from them (see also p. 371).

It has been made clear that in mammals the purins may be derived from ingested nucleoproteins, but this cannot be the only source, since purins are found in the urine during starvation and on a diet free from purins. This indicates a constant production of these substances in metabolism. Uric acid and purin bases from this source have been termed *endogenous* by Burian and Schur, in contradistinction to those which are eliminated after the ingestion of nuclein-containing food, which are called *exogenous*.

Burian and Schur[3] also established the fact that while the endogenous uric acid elimination varied between 0.3 and 0.6 gram daily, according to the individual, it did not vary in the same individual, but was a constant factor in his metabolism.

A purin-free diet is obtained by giving such articles of food

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[1] Thannhauser and Bommes: "Zeitschrift für physiologische Chemie," 1914, xci, 336.

[2] Kossel: *Ibid.* 1886, x, 248.

[3] Burian and Schur: "Pflüger's Archiv," 1901, lxxxvii, 239.

as milk, eggs, bread, potatoes, fats, and sugars, none of which contain nuclear material which forms exogenous purins in the body. Burian and Schur found that on such a diet the uric acid elimination was entirely independent of the quantity of protein ingested. It has been demonstrated by Rockwood[1] that the endogenous uric acid elimination is independent of the calorific value of the diet. Addition of 500 calories contained in maple sugar to a diet containing 2500 calories did not affect the excretion of uric acid. Rockwood's experiments extended over a long period of time. His individuals were nourished on milk, eggs, white bread, crackers, cheese, apples, and butter. The constancy of the uric acid output in the same individual is seen in the following table—in one case the record covering nearly a year:

TABLE SHOWING THE CONSTANCY OF THE DAILY ENDOGENOUS URIC ACID EXCRETION IN THE SAME INDIVIDUAL (TWO SUBJECTS)

Person A.	Date, 1903.	Urine N in Grams.	Uric Acid, Grams.
	January	11.99	0.308
	February	11.58	0.305
	March	11.15	0.315
	May	12.63	0.321
	July	12.68	0.313
	November	9.99	0.298
Person B.	January	13.41	0.478
	March	13.92	0.452

This total shows the constancy of the output of endogenous uric acid in the same individual during a long period. Here the difference in the behavior of two individuals may be ascribed to a personal idiosyncrasy as regards the capacity of producing uric acid. From the record of Chittenden's[2] experiments, which covered a period of twenty-one months, it may be observed that a very low protein diet and moderate intake of food were without effect on the output of uric acid.

The source of the endogenous purins has been the cause of considerable speculation. In birds there is a large synthetic

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[1] Rockwood: "American Journal of Physiology," 1904, xii, 38.

[2] Chittenden: "Physiological Economy in Nutrition," 1904, p. 24.

production of uric acid in the liver, for Minkowski[1] has shown that extirpation of the liver in geese leads to a replacement of uric acid by ammonia and lactic acid in the urine. The following analyses[2] give an idea of the composition of the urine of birds:

	Duck's Urine. (Total N = 0.615 gm.) Per Cent.	Fowl's Urine. (Total N = 0.759 gm.) Per Cent.
Ammonia	3.20	1.49
Urea	4.19	0.99
Uric acid	77.88	85.86
Purins	0.53	1.69
Colloidal N	4.09	
Amino-acid	2.71	2.52
Unknown	7.40	7.45
	100.00	100.00

The method of the synthetic production of purins is entirely conjectural.

Ingestion of pyrimidin bases (p. 528) has failed to yield purins in the organism.[3]

Burian[4] has investigated the source of the endogenous purins and comes to the conclusion that only a small part of the endogenous uric acid arises from the nucleoproteins of cellular tissue or those of dead leukocytes. It would require too large a destruction of tissue to provide from 0.3 to 0.6 gram uric acid or 0.1 to 0.2 gram purin nitrogen daily in the urine if it all arose from cell nuclein.

Burian and Schur's[5] analyses, showing the content of purin nitrogen in various tissues, are given below:

TABLE SHOWING THE QUANTITY OF PURIN N CONTAINED IN 100 GRAMS OF DIFFERENT ANIMAL TISSUES

	Total Purin N.	N in Free Purin Bases.
Meat	0.06	0.045
Thymus	0.45	0.05
Calf's liver	0.12	0.033
Calf's spleen	0.16	0.046

[1] Minkowski and Naunyn: "Archiv für experimentelle Path. und Pharm.," 1886. xxi, 41.

[2] Szalágyi and Kriwuscha: "Biochemische Zeitschrift," 1914, lxvi, 126.

[3] Steudel: "Zeitschrift für physiologische Chemie," 1903, xxxix, 136.

[4] Burian: *Ibid.*, 1905, xliii, 532.

[5] Burian and Schur: "Pflüger's Archiv," 1900, lxxx, 308.

To obtain the amount of endogenous uric acid present in the urine, if it were produced by the destruction of nucleoproteins, it would be necessary to destroy completely a quantity of nucleoprotein equal to that contained in more than 100 grams of liver. It does not seem possible that nuclein destruction or nuclein metabolism could reach this extent.

Burian concludes that in the resting muscle there is a constant production of hypoxanthin which is converted into uric acid through the activity of the xanthin oxidase. In the active muscle there is a greater production of hypoxanthin which is not completely oxidized on account of a local oxygen deficiency.

It had been found by many previous observers that exercise has no effect on the purin excretion in the urine of twenty-four hours in man. Burian, however, finds a large increase in the purin elimination for an hour or two after severe muscular exercise, and this is followed by a compensatory reduction in the output during those subsequent hours which represent the interval of weariness in the muscle.

These observations were confirmed by the work of Rockwood,[1] who saw that the purin excretion was less during the night than during the day, and by the work of Pfeil,[2] who found a constant morning rise in the output of purins in human urine.

These facts confirm Burian's contention that the most general source of endogenous purins is a constant production of hypoxanthin in muscle, a production which varies with the individual and is possibly proportional to the mass of his musculature. Comparable to this is the constant production of creatinin (p. 209). Such of the purin bases as escape oxidation may be excreted by the blood flowing through the kidney even as uric acid is excreted under the same circumstances.

Sivén[3] does not believe that muscular work appreciably raises the production of endogenous purins. He thinks that

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[1] Rockwood: *Loc. cit.*

[2] Pfeil: "Zeitschrift für physiologische Chemie," 1904, xl, 1.

[3] Sivén: Abstract in "Zentralblatt für Stoffwechsel," 1906, i, 81.

the reduction in purin elimination during the night time is due to general inactivity of all the tissues, and shows that when an evening meal containing much protein is taken and the kidney is made thereby to functionate during the night, then the purin elimination is increased. Burian's discovery of increased elimination during work was perhaps due to the fact that the work was accomplished during the morning hours, when an increased elimination due to purins retained during the night would normally occur.

Mendel and Brown[1] have determined the hourly excretion of uric acid as influenced by the ingestion of meat, liver, and other animal tissues. The increase in the eliminated uric acid is very marked and reaches a maximum two or three hours after the ingestion of these animal tissues. Thus after the ingestion of 600 grams of chopped meat the uric acid elimination, which had been 19 milligrams, rose during the following three hourly periods to 28, 88, and 98 milligrams, and then fell in successive hours to 79, 73, 51, 36, 25, and 22 milligrams. It will be seen later that such curves of exogenous uric acid excretion do not occur in the gouty patient in whom there is uric acid retention (see p. 548).

The recent studies of Stanley Benedict[2] concerning the uric-acid content of the blood have brought to light some new and important facts. Fowl's blood had heretofore been accounted much richer in uric acid than ox blood. Benedict finds this to be true only of the blood-serum, which in the fowl contains uric acid which circulates uncombined, whereas the blood-serum of the ox is almost entirely free from uric acid. Considered as a whole, however, ox blood yields 0.50 milligram of uncombined uric acid in 100 c.c. of blood. This is the amount which had been previously reported, but after hydrolysis 6.7 milligrams of uric acid were isolated and identified. This is entirely contained in the corpuscles and amounts to 50 per cent. more than the uric acid content of chickens'

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[1] Mendel and Brown: "Journal of the American Medical Association," 1907, xlix, 896.

[2] Benedict, S. R.: "Journal of Biological Chemistry," 1915, xx, 633.

blood. These results throw additional light upon Minkowski's conception of the nature of gout, soon to be considered.

The subject of gout is one of the most baffling in the literature of metabolism. Despite the brilliant work upon the purins during the last ten years, work which has been illuminated by the discovery of the formula of nucleic acid by Levene, the nature of gout remains as much of a mystery as ever.

Just as the whole trouble in diabetes turns upon the inability of the organism to destroy sugar, so the symptoms manifested in gout are dependent upon the deposit of acid urate of sodium in certain localities. One of the earliest descriptions of gout comes from Sydenham, who suffered for forty years from the disease and published an extended account of it in 1683. It was Garrod[1] who first established the fact that uric acid was present in the blood of gouty persons. He believed that this excess of urate was the cause of gout, the excess being deposited from the blood in the joints in the form of crystals. The problem of metabolism in gout is a problem of the factors entering into the cause of this deposit of urate. The general metabolism, exclusive of the purin factor, is exactly the same as in health. Magnus-Levy[2] proved that the oxygen absorption and carbon dioxid elimination is the same in gout as in health. The cause of the trouble must be sought elsewhere than in a reduced general oxidation power of the tissues.

Clinical experience teaches that the predisposing causes are excessive eating, little muscular exercise, the abuse of alcoholic beverages, and lead-poisoning.

Beebe[3] has administered alcohol in various forms to a normal individual. He finds that even large doses have no

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[1] Garrod: "The Nature and Treatment of Gout," 1859.
[2] Magnus-Levy: "Berliner klinische Wochenschrift," 1896, xxxiii, 416.
[3] Beebe: "American Journal of Physiology," 1904, xii, 13.

effect on the hourly excretion of uric acid in a fasting man. The endogenous purin metabolism is therefore unchanged by the ingestion of alcohol. It is important to know that alcohol is apparently without effect upon such part of the purins as may be directly derived from cell metabolism. Further investigation of this subject by Landau[1] has revealed the fact that the influence of alcohol is different in different individuals, and that usually there is a slight increase in the output of endogenous purins after taking alcohol. Mendel and Hilditch[2] report the same results. Administration of alcohol equal to 500 calories, together with a purin-free diet, to a man previously unaccustomed to alcohol caused a slight decrease in the elimination of nitrogen and a slight increase in that of uric acid. Otherwise the urinary analysis showed little or no change, even when alcohol was administered for weeks.

Pollak[3] has shown that in chronic alcoholics the retention of ingested purins is favored.

Minkowski,[4] with a master hand, summarized modern knowledge concerning gout as follows:

1. The deposit of urate in the tissues is the first change which takes place in the formation of the specific gouty nodules. These tissues are not necrotic, as taught by Ebstein.
2. The tissue changes in the vicinity of the gouty nodules are in part due to mechanical, in part to chemical or osmotic, action, caused by the precipitated urates.
3. The acute inflammation in gout, as observed during the attack, is produced in the vicinity of the urate deposits through some unknown cause. Traumatic, toxic, or infectious elements appear to be collectively active in this regard. The attack probably constitutes the reaction of the organism to rid itself of uric acid, an effect which is only partly realized.

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[1] Landau: "Deutsches Archiv für klinische Medizin," 1909, xcv, 280.

[2] Mendel and Hilditch: "American Journal of Physiology," 1910–11, xxvii, 1.

[3] Pollak: "Deutsches Archiv für klin. Med.," 1906, lxxxviii, 224.

[4] Minkowski: von Leyden's "Handbuch der Ernährungstherapie," 1904, ii, p. 277.

4. An accumulation of uric acid in the blood is a constant accompaniment of gout.

5. The increased quantity of uric acid in the blood must not be considered as the cause of the precipitation of urates in the gouty nodules. There must be certain local influences which favor the deposit of urates; for Klemperer has shown that the blood of gouty patients may dissolve much more uric acid than is actually present in it; and again, the blood in leukemia may contain as much uric acid as in gout, without there being any indication of a deposit of urate.

6. The uric acid elimination is the same in the gouty as in the normal person, except at the time of the attack. Before the attack there is retention, but during and after the attack an increased excretion of uric acid in the urine.

7. The accumulation of uric acid in the blood is not due to a diminished oxidation of uric acid, but rather to a diminution in the quantity excreted in the urine.

8. It is not certain that the lessened excretion of uric acid is due to a disturbance of renal function. Very likely it depends upon the presence of uric acid in some abnormal chemical union. This abnormal substance may be with difficulty eliminated in the urine, but may lend itself readily to the formation of tophi (p. 532).

9. The ultimate cause of the unusual behavior of uric acid in gout is probably an abnormal metabolism within the nuclei of the cells, where the nucleic acid content is the means of solution and conveyance not only of the purin bases but also of uric acid.

The opinions of other modern workers vary somewhat from those of Minkowski, as appears in the following:

Almagia,[1] in Hofmeister's laboratory, has performed some interesting experiments and concludes that the older view of Garrod is correct—that is, that an excess of urates in the blood is the cause of gout. Almagia finds that thin strips of cartilage suspended in dilute neutral solutions of sodium urate absorb

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[1] Almagia: "Hofmeister's Beiträge," 1906, vii, 466.

the salt, do not destroy it, but cause it to be deposited in fine crystals within the cartilage. He furthermore injected 5 to 7 grams of uric acid into the peritoneal cavity of rabbits, a dose which usually killed them. On testing the liver, spleen, muscles, and lungs with the murexid test for uric acid, negative results were obtained, whereas cartilage gave a positive reaction indicating the presence of urates. Almagia concludes that the deposit of urates in the cartilage of a gouty patient is but the result of a temporary or permanent increase in the uric acid content of the blood. The liability of cartilage to contain deposits of urates has received no satisfactory explanation. Exposure to cold, stagnation of the blood flow, and the richness of cartilage in sodium salts have been suggested as possible reasons for the precipitation of the urates.

In leukemia, where there must be a large destruction of nucleoprotein, as evidenced by a report concerning a patient who eliminated 12 grams of uric acid during the last forty hours of life, there is no gout.[1] Folin reports that normal human blood contains about 1.5 to 2.5 milligrams of uric acid per 100 c.c. and that this quantity is exceeded not only in gout but also in leukemia, lead-poisoning, and in nephritis. Folin and Denis[2] state that in true gout there is no increase in the quantity of non-protein nitrogen in the blood, though this increase appears in arthritis deformans. They recommend this as a means of differential diagnosis between gout and arthritis.

Magnus-Levy,[3] Vogt,[4] and Reach[5] were the first to discover that the administration of glands rich in nucleoprotein, such as thymus and pancreas, to gouty persons did not cause as large an excretion of uric acid in the urine as when the same amounts of these materials were given to normal individuals.

The work of Soetbeer[6] is of the best modern character, and

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[1] Magnus-Levy: "Virchow's Archiv," 1898, clii, 107.
[2] Folin and Denis: "Archives of Internal Medicine," 1915, xvi, 33.
[3] Magnus-Levy: "Zeitschr. für klin. Med.," 1899, xxxvi, 414.
[4] Vogt: "Deutsches Arch. für klin. Med.," 1901, lxxi, 21.
[5] Reach: "Münchener med. Wochenschr.," 1902, xlix, 1215.
[6] Soetbeer: "Zeitschrift für physiologische Chemie," 1904, xl, 54.

illustrates the retention of uric acid in gout. Soetbeer compared the excretion of uric acid by gouty people during three-hour intervals with that of normal individuals, as observed by Pfeil (p. 542). In one case of long-standing gout, of light character and with long intervals between the attacks, there was little variation from the normal in the uric acid excretion. In another case of gout, a patient who was examined between the attacks showed no increase in uric acid output after changing from a purin-free diet to one containing 320 grams of meat, and showed only a slight increase in elimination after 640 grams of meat were given. These results were obtained six weeks after the last attack and at a time when the patient was entirely free from pain. In still another case 350 grams of meat were given during the attack to a gouty patient who had no fever and whose urine was free from albumin and sugar. The results were as follows:

	Uric Acid in Grams.
Diet free from purins	0.276
" " " "	0.328
Diet + 350 grams meat	0.316
" " " "	0.270
" " " "	0.255

In this experiment even during the days of purin-free diet there was no "morning rise" noted as a normal incident by Pfeil. The hourly uric acid excretion was very even. The kidney was apparently removing uric acid up to the limit of its capacity.

Hefter[1] administered uric acid subcutaneously to a gouty patient and recovered only 11 per cent. of it in the urine in contrast with a recovery of 86 per cent. in the normal individual. Thannhauser and Bommes[2] report that although between 75 and 82 per cent. of the purin content of 1 gram of adenosin when subcutaneously administered to normal men appears as uric acid in the urine, and the uric acid content of

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[1] Hefter: "Deutsches Archiv für klin. Med.," 1913, cix, 322.

[2] Thannhauser and Bommes: "Zeitschrift für physiologische Chemie," 1914, xci, 336.

the blood does not rise, yet in severe gout this procedure is not followed by additional excretion of uric acid, though uric acid does increase in the blood. Three of four gouty patients had attacks of gout after this treatment. The authors state that the conclusion is unavoidable, that gout is due to a disturbance in the elimination of uric acid.

Denis[1] finds that there is no increase in the uric acid content of the blood of man after the ingestion of foods rich in purins, except in cases of renal insufficiency.

The drugs which are used in rheumatism, arthritis, and gout, such as salicylate of soda, aspirin, and atophan, cause an increased elimination of uric acid in the urine and a concomitant fall in the quantity of uric acid present in the blood.[2] Salicylate of sodium when given in amounts to produce no salicylate intoxication (such as ringing in the ears) has no effect upon the basal metabolism of normal men, though the uric acid and total nitrogen elimination is somewhat increased.[3]

The discovery of Stanley Benedict of the large amount of uric acid combined in the corpuscles of ox blood lends added significance to the idea of Minkowski that the deposition of urates in gout may be dependent upon some abnormal chemical union of the uric acid which breaks up, yielding urates for the construction of tophi. The possible importance of this factor should not be lost sight of.[4]

Miller and Jones[5] were unable to find any variation from the normal in the distribution of the purin enzymes in the tissues of a gouty individual.

Linser[6] tells how a gouty individual suffering from eczema was treated with the Röntgen rays. Although the person was on a purin-free diet, the treatment invariably brought on an

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[1] Denis: "Journal of Biological Chemistry," 1915, xxiii, 147.

[2] Jackson and Blackfan: "Albany Medical Annals," 1907, xviii, 24; Rockwood: "American Journal of Physiology," 1909–10, xxv, 34; Fine and Chace: "Journal of Biological Chemistry," 1915, xxi, 371; Denis: "Journal of Pharm. and ex. Ther.," 1915, vii, 601.

[3] Denis and Means: "Journal of Pharm. and ex. Ther.," 1916, viii, 273.

[4] Minkowski: "Zeitschrift für physiologische Chemie," 1913, lxxxviii, 159.

[5] Miller and Jones: *Ibid.*, 1909, lxi, 395.

[6] Linser: "Therapie der Gegenwart," 1908, No. 4.

attack of gout on account of the increased production of uric acid within the body which normally follows such treatment.

Gudzent[1] states that monosodium urate occurs in the blood in two isomeric forms, the more soluble *lactam* form being readily convertible into the less soluble and more stable *lactim* form, these having been chemically differentiated by Emil Fischer. While 100 c.c. of blood dissolve 18.4 milligrams of the first salt, they dissolve only 8.4 milligrams of the second. Gudzent[2] maintains that the inhalation of radioactive emanations leads to an increased elimination of uric acid in the gouty, due to the conversion of the lactim form of uric acid into the lactam form. However, Wiechowski[3] denies the influence of radium upon the solubility of uric acid, though he finds that the emanations bring about a rise in the elimination of uric acid not only in gouty persons but also in normal individuals. He believes with His that the emanations may reduce the inflammatory processes in gout, thereby indirectly favoring more normal conditions and leading to the elimination of uric acid. There is little or no influence exerted by radium emanations upon the respiratory metabolism,[4] although it is stated that the ingestion of one hundred times the usual therapeutic dose has caused an increase in metabolism of 17 per cent.[5]

Von Noorden and Schliep[6] suggest that gouty patients be tested for their "tolerance" for purin bodies just as diabetics are tested for their tolerance for carbohydrates; 400 grams of meat contain 0.24 gram of purin nitrogen, which is the equivalent of 0.72 gram uric acid. A patient was put on a purin-diet free; was given 400 grams of meat, then put on a

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[1] Gudzent: "Zeitschrift für physiologische Chemie," 1909, lxiii, 455.

[2] Gudzent: "Zeitschrift für klin. Med.," 1910, lxxi, 304; 1913, lxxviii, 266.

[3] Knaffl-Lenz and Wiechowski: "Zeitschrift für physiologische Chemie," 1912, lxxvii, 303.

[4] Silbergleit: "Berliner klinische Wochenschrift," 1908, xlv, 13; 1909, xlvi, 1205.

[5] von Benczúr and Fuchs: "Zeitschrift für ex. Path. und Ther.," 1912–13, xii, 564.

[6] von Noorden and Schliep: "Berliner klinische Wochenschrift," 1905, xlii, 1297.

purin-free diet again, and afterward was tested with 200 grams of meat. The results were as follows:

Day.	Diet.	Uric Acid in Grams.
4	Purin free	0.462
5	" " + 400 gm. meat	0.522
6	" " + 400 gm. meat	0.544
7	" "	0.539
8	" "	0.528
9	" "	0.458
10	" " + 200 gm. meat	0.549
11	" " + 200 gm. meat	0.655
12	" "	0.647
13	" "	0.499
14	" "	0.433

The authors conclude that while the increased uric acid output after giving 400 grams of meat is not what it would be normally, yet after giving 200 grams the quantity of additional uric acid is fully eliminated. Hence this patient had a tolerance for the purins in 200 grams of meat.

Dietetic rules for gouty sufferers are intended to combat the fundamental anomalies of the metabolism. The organism must not be overloaded with uric acid. Minkowski's rules[1] for treatment of gout may be thus abstracted: Sweetbreads, liver, and kidney are to be strictly excluded from the diet since they contain purin bases in large quantity. Meat is to be taken in moderation only. Wine should be taken sparingly or not at all, and beer rigidly excluded on account of the nuclein in yeast. Cathartics may be given to rid the intestine of purin bodies excreted into the intestinal canal, and water-drinking, which promotes a larger flow of urine and increased uric acid elimination, is strongly to be commended. The diet for a gouty patient should contain each day 100 or 120 grams of protein, 80 or 100 grams of fat, and 250 or 300 grams of carbohydrates (2200 to 2600 calories). This should not include more than from 200 to 250 grams of meat per day. Indigestible cakes, pies, rich foods, and heavy salads should be forbidden. Moderation and self-control are the watchwords for the gouty sufferer.

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[1] Minkowski: "Deutsche medizinische Wochenschrift," 1905, xxxi, 409.

It is impossible to oxidize uric acid, and no treatment now known increases its solubility. Minkowski hopes that some organic compound may be discovered which will accomplish this purpose.

Bearing the facts of the above discussion in mind, the reader will comprehend that present-day doctrines concerning metabolism in gout may shortly become entirely obsolete through new and far-reaching discoveries.

CHAPTER XX

THE INFLUENCE OF CERTAIN DRUGS UPON METABOLISM

Important work concerning the influence of certain drugs upon the basal metabolism in normal men has been carried out by Higgins and Means[1] in Edsall's clinic at Boston. They present a summary of their findings in the following table:

THE INFLUENCE OF DRUGS ON METABOLISM

Drug.	Average Dose.	Action.				
		Respiratory Center.	Bronchial Musculature.	Metabolism.	Respiration Rate.	Pulse-rate.
Atropin	1.0 mg.	None.	Dilation.	Increase.	None.	Fall, then rise.
Caffein	0.4 gm.	Stimulation.	Either dilation or none.	Increase.	Increase.	None.
Camphor	0.1 gm.	None.	Either dilation or none.	Generally slightly increased.	None.	None.
Strychnin	4.5 mg.	None.	Probably none.	None.	None.	None.
Morphin	16.0 mg.	Either depression or none.	Constriction.[*]	Either slight decrease or none.	Slight increase.[†]	None or decrease.
Heroin	5.0 mg.	Depression.	Constriction.	None.	None.	Slight decrease.

[*] Or none, when the bronchi are already constricted.

[†] This obviously does not apply to large doses of morphin.

They report that caffein caused a rise in the metabolism equal to 15 per cent. without changing the pulse-rate. The increase after camphor was 8 per cent. and after atropin only 4 per cent. above the normal basal metabolism. That therapeutic doses of strychnin cause no increase in metabolism is significant.

[1] Higgins and Means: "Journal of Pharmacology and Experimental Therapeutics," 1915, vii, 1.

Unpublished results of Means, Aub, and DuBois show that large doses of caffein given to normal individuals cause an increase in the basal metabolism of 10 to 30 per cent. without increasing the pulse-rate or the body temperature.

Other unpublished data from the Russell Sage Institute of Pathology, and taken from investigations by Eggleston and DuBois, show that no change in metabolism occurs in cardiac cases after the administration of full therapeutic doses of digitalis which markedly reduce the heart rate.

The influence of large doses of caffein appears at first thought to be remarkable, the basal heat production rising to the level found after the ingestion of large quantities of meat. The increase is slight, however, when compared with the stimulation of metabolism by muscular exercise. It appears great only when compared with the immutability of the level of the normal basal metabolism, a state in which the heat production is subservient to the requirement of energy on the part of the cells for the maintenance of life, the requirement being so regulated and adjusted that the heat loss per square meter of surface is approximately 40 calories per hour, while the body temperature is maintained at a constant level.

CHAPTER XXI

FOOD ECONOMICS[1]

THE consideration of the food supply from a national standpoint was forced upon Germany at the outbreak of the great war which is now in progress. Eminent scientists combined in a report upon the prospects of the sustenance of the nation. Imports from oversea had been restricted. Meat, butter, cheese, and fish formerly obtained from Holland and Denmark were no longer available. The North Sea fisheries which had yielded 179,000 metric tons (1 metric ton = 2200 lbs.) of fish were closed, trained farm hands were fewer, crops in East Prussia and Alsace had been destroyed, the situation appeared serious. It was estimated that the annual amount of food fuel necessary to support 68,000,000 Germans —men, women, and children—was 56,750,000,000,000 calories. This is the equivalent of 3000 calories per adult per day. The quantity of protein required in this fuel, if the human machines were to maintain themselves in self-repair, was estimated to be 1,605,000 metric tons per annum. It was calculated that a mixed population of 68,000,000 men, women, and children required the same amount of food as would 51,823,000 adults.

In order to increase the production of food and to diminish the waste the committee recommended increasing the crop of beans, with its large protein content, reducing the unnecessarily large meat supply, and increasing the intake of cheese and skimmed milk, which latter should no longer be fed to pigs, improving the yield of vegetables and fruits, and reducing the quantity of butter and cream produced.

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[1] The first pages of this chapter are a revision of a paper published in the "Journal of the Washington Academy of Sciences," 1916, vi, 387.

A reduction in the consumption of meat, butter, and cream was necessary because edible grains would be required for human food, and the maintenance of the usual number of cattle was no longer deemed possible.

The estimated savings as above enumerated would result in a total production of 81.25 billion food calories containing 2,022,800 tons of protein.

The conditions were thus summarized:

TABLE SHOWING THE ANNUAL FOOD REQUIREMENTS OF 68,000,000 PEOPLE IN GERMANY

	Protein in 1000 Metric Tons.	Calories in Thousand Millions.
Actual requirement	1605	56.75
Used before the war	2307	90.42
Available (unchanged habits)	1543	67.86
Available (under present recommendations)	2023	81.25

From these data it was concluded that the German people, through co-operation of millions of inhabitants, would be able to prevent suffering for lack of food.

The writer is informed upon good authority[1] that the food produced during 1914–16 never attained the level of production in peace times, that the food requirement of the population was underestimated for the physical work to be accomplished and underestimated for those who were in the period of adolescence; furthermore, that the enforcement of the food laws was placed in the hands of farmers, middlemen, and politicians, who mismanaged the situation.

It is not unimportant to know something of the cost of these great quantities of food fuel.

If one takes as a basis the wholesale cost in the United States of food as purchased on account of the Commission for Relief in Belgium one can estimate in the terms of the cost of various simple food-stuffs the lowest wholesale cost of the yearly food fuel requirement of the German nation as follows:

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[1] A. E. Taylor: Oral communication, quoted by permission.

WHOLESALE COST IN THE UNITED STATES OF FOOD FUEL FOR 68,000,000 PEOPLE

	Cost per Pound.	Cost per 1000 Calories.	Cost for 56,750,000,000 Calories.
Cornmeal	$0.016	$0.011	$ 634,000,000
Wheat	0.023	0.014	794,500,000
Rice	0.03	0.018	1,022,500,000
Flour	0.033	0.02	1,135,000,000
Beans	0.045	0.029	1,634,000,000

The wholesale cost of sufficient food fuel exclusively in the form of beans to provide for 100,000,000 men, women, and children in the United States for a period of one year, computed on the basis of 3000 calories daily for each adult, would call for a sum of $2,500,000,000. Beans are more costly than rice and wheat, but have a larger protein content.

In this connection it is interesting to consider the living expenses of a poor family in New York City.

Family, two adults, three children, wages $60 per month:

Rent	$15.00
Food	25.00
Coal	4.50
Insurance	2.25
Soap, matches, etc.	1.00
Clothing and extras	12.25
	$60.00

To the man of large affairs the expenditure of $25 a month for food appears of little moment, and yet if the 100,000,000 inhabitants of the United States lived as this typical poor man's family lived the cost of food would aggregate $6,000,000,000 per annum. To any man of large affairs the maintenance at Boston of the Nutrition Laboratory of the Carnegie Institution with its budget of about $50,000 per annum appeals impressively to the imagination, and yet this work is accomplished at an expense of less than $\frac{1}{1000}$ of 1 per cent. of what the American people would pay for food if each family of 5 had an income of $720 per annum. It may be further remarked that this estimated cost of food for the nation is twice the amount of the gross earnings of all the railways in the United States.

Is it not a little sad to think that the expenditure of thousands of millions of dollars annually for food, an expenditure frequently amounting to more than half of the income of the poor man, should take place without any real idea as to what the nature of food is?

F. C. Gephart[1] of the Russell Sage Institute of Pathology, has made a study into the food consumption of the boys at St. Paul's School at Concord, New Hampshire, one of the largest private boarding-schools in the country. The total annual food supply may be thus computed:

SUPPLIES FOR BOYS' BOARDING SCHOOL

	Protein, Metric Tons.	Fat, Metric Tons.	Carbohydrate, Metric Tons.
Food supply	20.5	25.6	60.5
Waste	3.8	5.4	4.2
Food-fuel	16.7	20.2	56.3

This quantity of nourishment was taken by 355 boys and also about 100 adults (masters and servants). This quantity of food when computed on the basis of the individual meals served appears as follows:

	Food Supply per Meal.			
	Pounds.	Grams.	Calories,	Calories Per Cent.
Protein	0.1107	50.2	206	14*
Fat	0.1332	60.4	562	39
Carbohydrates	0.3717	168.8	692	47
			1460	100

* 70 per cent. of this is in animal protein.

The cost of this food per meal was 20 cents, or 13.8 cents per 1000 calories. The food, which was bought by a purchasing

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[1] Gephart: "Boston Medical and Surgical Journal," 1917, clxxvi, 17.

agent in the Boston market, was of the best quality, and included 193 separate varieties.

Such a dietary taken by the 100,000,000 inhabitants of the country would cost per annum $11,500,000,000 if the German minimum of 3000 calories daily per adult be allowed. This cost is twice what the poor man in New York City pays for his food.

These growing, athletic boys, however, were not satisfied with 3000 calories daily. They not only took 4350 calories daily at the table, but they bought 650 additional calories in food at a neighboring store, the principal item being chocolate.

Data concerning the subjects of the investigation are epitomized in the two following tables:

TABLE SHOWING THE NUTRITION CONDITIONS AT A SCHOOL CONTAINING 355 BOYS

	Average Age.	Height.	Weight.	Body Surface.	Basal Metabolism (Calc.).	Food.	Food in Per Cent. of Basal.
	Years.	Cm.	Kg.	Sq. M.	Cals.	Cals.	
The Upper School......	16	172.7	60.6	1.73	1826	4997	274
The School....	14½	165.1	50.8	1.54	1737	5126	295
The Lower School......	13½	157.5	43.8	1.40	1647	4949	300

The basal requirement of boys is, as DuBois (see p. 129) has shown, 25 per cent. above that of the adult. The total fuel intake was three times that of this basal level which is the heat production when a boy is resting or asleep. The 5000 calories contained in the ingesta is half as much again as a farmer at work would require. The quantity of the calculated intake would certainly not be lowered by excluding the adults who unavoidably entered into this computation. These data explain the ravenous appetite of boys. Lack of appreciation of this factor or lack of provision for it are the probable causes of much of the undernutrition seen in children of school age.

The distribution of the fuel values among the various more common articles taken as food at the school is shown in the following table:

PERCENTAGE DISTRIBUTION OF THE CALORIES INGESTED AT A BOYS' BOARDING SCHOOL

	Per Cent.		Per Cent.
Bacon	1.8	Lamb	5.3
Beef	6.7	Milk	12.6
Bread and flour	13.3	Pork loins	1.1
Butter	11.2	Potatoes	5.9
Cream	1.3	Sugar	11.6
Eggs	2.3	Other items	24.5
Fowl	1.9		

It is interesting that twelve dietary items yield 75 per cent. of the fuel value and that 181 other varieties yield the remaining 25 per cent. Bread, butter, milk, and sugar together yield 50 per cent. of the food fuel.

According to the German minimum allowance an average family of 5—father, mother, and three children—would require 11,400 calories in food daily. If the family's dietary were based proportionately upon that of the boys' school it would cost as follows, provided its food supplies were purchased on Second Avenue, New York City:

	Calories.	Cost in Cents.
Total food	11,400	
Bread	1,500	5
Butter	1,500	15
Milk	1,500	16
Sugar	1,500	4
	6,000	40

Forty cents will buy more than half the family's food requirements at an average cost of 6⅔ cents per 1000 calories instead of 14 cents, the average cost at the school. If $25 is spent each month for food, 80 cents a day is available, or 7 cents for 1000 calories. The margin is narrow.

It would be well if the family knew that more than half its food supply could be had for 40 cents a day, and that this bread, butter, milk, and sugar was of equal nutritive value to the best the country affords. The remaining 5400 calories could then be bought at a cost of 8 cents per 1000. This sum will purchase most of the usual food-stuffs, with the exception of meat.

As a matter of statistics the annual consumption of cane-sugar in the United States in 1912–13 reached 85.4 lbs. per capita, which is the equivalent of 2000 calories daily for a family of 5, or 20 per cent. of the energy requirement. This quantity of sugar costs the nation $1,500,000 daily, and the rich harvest to be reaped by substitution of only a small part of this by saccharin, which has no fuel value whatever, is obvious.

It has appeared to those at work in the laboratory that it would be of great importance to associate the caloric value of food with cost in dollars and cents.

For the understanding of this the following table has been prepared showing the cost of 2500 calories, which is the energy requirement of an average adult of sedentary occupation.

WEIGHTS AND COSTS OF VARIOUS FOODS NECESSARY TO FURNISH 2500 CALORIES

(Prices at Second Avenue and 90th Street, New York City, Early in 1916)

Articles.	Weight.		Cost.
	Lbs.	Oz.	Cents.
Cornmeal	1	8	$.04\frac{1}{2}$
Hominy	1	8	$.04\frac{1}{2}$
Oatmeal	1	$5\frac{1}{2}$	$.05\frac{1}{4}$
Flour	1	8	.06
Sugar	1	$5\frac{1}{2}$	$.06\frac{23}{32}$
Rice (broken)	1	$8\frac{1}{2}$	$.07\frac{1}{4}$
Bread	2	1	$.08\frac{1}{4}$
Lard		$9\frac{1}{2}$	$.08\frac{5}{16}$
Corn syrup	1	13	$.09\frac{2}{3}$
Molasses	1	15	$.12\frac{15}{16}$
Peanut butter		14	.14
Pork (fat)	1		.14
Beans (dried)	1	9	.14
Oleomargarin		11	$.15\frac{13}{16}$
Potatoes	8	1	$.16\frac{1}{8}$
Dates	1	12	$.17\frac{1}{2}$
Olive oil		$9\frac{1}{2}$	.19
Hickory nuts (unhulled)	2		.20
Raisins (dried)	1	12	.21
Apples (dried)	1	13	$.21\frac{3}{4}$
Cheese (American pale)	1	3	$.23\frac{3}{4}$
Butter		11	$.24\frac{1}{16}$
Brazil nuts (unhulled)	1	8	.27
Cocoa	1	1	$.29\frac{9}{16}$
Lentils	1	8	.30
Almonds (unhulled)	1	8	.36
Apples (fresh)	11	5	.38
English walnuts (unhulled)	1	13	$.41\frac{11}{16}$
Cod (salt)	6		.90

True food reform demands the sale of food by calories and not by pounds. Professor Murlin has advocated that the government compel manufacturers to place upon each can or package of food sold the caloric content of the package.

Besides fuel value it must be remembered that the body must have protein. The machinery of the living parts of the body such as muscle is in a constant state of wearing away. The wear and tear is slight, but protein must be taken in the food to replace that destroyed in the body, or the machinery of the cells will wear out and death from lack of protein will ensue.

Different proteins have different values for this purpose. Those of meat, fish, eggs, and milk will replace body protein part for part. Such proteins may be classified as proteins of Grade A. Gelatin has practically no power to replace body protein and should be classified as protein of Grade D. Wheat contains a mixture of proteins of Grades A and D in which those of Grade A predominate, so wheat may be classified as having a protein value of Grade B, whereas corn, from analogous reasoning, may be said to have a protein value of Grade C.

An ordinary dietary with a liberal allowance of protein contains 15 per cent. of its calories in that form. A can or package of food containing 15 per cent. of its calories in protein should have a star placed with the letter determination of the grade of protein. For example, the label on a can of corn should read "This can contains *x* calories, of which *y* per cent. are in protein of Grade C."

A further desirable statement would be whether or not the food-stuff sold contained the natural mineral constituents from the organic source from which it was derived.

The determination of the heat of combustion of a dried sample of food takes fifteen minutes. Probably three hours would suffice to make a complete analysis by a government expert. The manufacturer should send his sample to the Bureau of Chemistry at Washington, declaring that to be his standard, and requesting information regarding his label. He should pay for this analysis as a patentee pays for his patent. If the government at any time should find the manufacturer selling a material on the market of character different from the standard deposited with the government, the manufacturer should be heavily fined.

It is not possible to consider the details of the great amount of extremely valuable work accomplished by the scientific departments of the Washington Government and in the individual Agricultural Experiment stations in this country and abroad.

It may, however, be of interest to present the results of a study of the sale of food at the Childs restaurants[1] in order to show this principle of caloric feeding, now adopted in hospitals and upon farms, that it may be worked out in the daily life of the people.

THE COST, INCLUSIVE OF RESTAURANT SERVICE, OF 2500 CALORIES IN FOODS ARRANGED IN ORDER OF THEIR INCREASING PRICE

(Note that when three portions furnish 2500 calories, one portion affords a good meal. When nine portions furnish 2500 calories, then three portions should form the meal.)

Name of Food.	Nutritional Calories for Five Cents.	Per Cent. in Bread and Butter.	Cost of 2500 Calories.	No. of Orders to Make 2500 Calories.
Napoleon	453.6	....	$0.28	6
Crullers	444.0	....	.28	6
Cabinet pudding and vanilla sauce	399.5	....	.31	6
Cocoanut pie	372.9	....	.34	7
*A—Roast beef sandwich with roll	357.8	....	.35	7
Bath buns	357.5	....	.35	7
Bread custard pudding	355.4	....	.35	7
Pineapple pie	347.4	....	.36	7
Corn muffins	342.2	....	.37	7
Apple pie	337.2	....	.37	7
New England pudding with vanilla sauce	330.7	....	.38	8

* Contains 15 per cent. or over of heat in protein. "A" contains the protein of meat, milk, eggs, or cheese.

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[1] Gephart and Lusk: "Analysis and Cost of Ready-to-serve Foods," published by "American Medical Association," 1915.

Name of Food.	Nutritional Calories for Five Cents.	Per Cent. in Bread and Butter.	Cost of 2500 Calories.	No. of Orders to Make 2500 Calories.
Chocolate spiced cakes	324.0	....	$0.39	8
Walnut layer cake with marshmallow icing	323.2	....	.39	8
Milk crackers	317.1	....	.39	8
Bread pudding with vanilla sauce	298.4	....	.42	8
Pumpkin pie	296.1	....	.42	8
A—Lamb croquettes and mashed potatoes	291.4	29.5	.43	3
Coffee cake	290.2	....	.43	9
Rhubarb pie	286.8	....	.44	9
A—German meat cakes and French fried potatoes	284.5	27.2	.44	3
Old-fashioned molasses cake	281.9	....	.44	9
Lemon pie	279.7	....	.45	9
*A—Vienna roast with French fried potatoes	278.3	29.7	.45	3
Butter cakes	278.0	....	.45	9
Minced ham sandwich	277.3	63.8	.45	9
Pork and Boston beans	276.6	27.1	.45	3
Cornmeal cakes with maple cane syrup	275.2	....	.45	5
A—Ham croquettes	263.1	32.7	.47	5
Cold rice pudding	263.1	....	.47	9
Ham sandwich with roll	261.8	....	.48	10
Banana layer cake	253.4	....	.49	10
*A—Cream chipped beef on toast	249.2	....	.50	3
Cocoa	247.5	....	.50	10
*A—Roast beef cutlet with tomato sauce.	246.5	38.4	.51	3
*A—German meat cakes with lyonnaise potatoes	246.4	....	.51	3
*A—Swiss cheese sandwich	244.0	59.6	.51	10
* —Boston baked beans	240.3	34.2	.52	5
A—Vienna roast, spaghetti and potatoes	236.3	34.0	.53	4
Chocolate cornstarch with cream	231.6	....	.54	11
Wheat cakes with maple cane syrup	231.1	....	.54	5
Milk crackers and milk	230.5	....	.54	5
*A—American cheese sandwich	230.2	....	.54	11
* —New York baked beans	229.7	35.5	.54	5
Hot corn bread	228.6	....	.55	6
*A—Country sausage	227.7	....	.55	11
Indian pudding with maple sauce	227.2	....	.55	11
*A—Minced tongue sandwich with tea biscuits	225.6	....	.55	11
Cream roll	225.1	....	.55	11
A—Beef cakes with brown gravy and macaroni	224.8	35.1	.56	4
* —New York beans, on the side	223.4	....	.56	11
Graham crackers	223.3	....	.56	11
A—Broiled ham	223.1	....	.56	3
A—Roast beef hash, browned	222.1	36.9	.56	4

Name of Food.	Nutritional Calories for Five Cents.	Per Cent. in Bread and Butter.	Cost of 2500 Calories.	No. of Orders to Make 2500 Calories.
Oyster pie	220.4	....	$0.57	4
*A—Minced chicken sandwich	220.3	73.0	.57	11
Apple tapioca pudding	217.2	....	.57	11
Potato salad	217.0	38.4	.58	6
Chocolate layer cake	212.4	....	.59	12
*A—Breaded veal cutlet and tomato sauce	211.9	33.0	.59	3
Egg-plant fried in butter	208.7	....	.60	4
Buckwheat cakes with maple cane syrup	208.3	....	.60	6
A—Roast beef croquettes with macaroni	208.3	34.3	.60	4
A—Fried bacon with French fried potatoes	208.1	....	.60	3
A—Sardine sandwich	207.4	....	.60	12
*A—Minced ham sandwich with olives	206.8	....	.60	12
*A—Ham and New York beans	206.6	40.2	.61	4
Vanilla cornstarch with cream	206.5	....	.61	12
*A—Roast beef cutlet and mashed potatoes	205.7	38.3	.61	4
A—Lamb cutlet and mashed potatoes	205.4	36.9	.61	4
Cocoanut cake	204.6	....	.61	12
Cream cheese walnut sandwich	201.5	....	.62	12
* —New York baked beans with tomato sauce	201.5	34.8	.62	6
A—Ham and Boston beans	201.3	44.6	.62	4
A—Liver and onions with French fried potatoes	200.1	....	.62	3
*A—Beef stew	199.8	35.3	.63	4
*A—Pork and New York beans	198.7	38.5	.63	4
*A—Ham sandwich	198.3	73.2	.63	13
Rice croquette with bacon	196.2	43.4	.64	4
Baked apple with cream	196.0	....	.64	6
A—Frankfurters and potato salad	195.9	42.5	.64	4
* —Baked beans with macaroni	195.8	....	.64	4
Cup of coffee (containing cream and sugar)	195.2	....	.64	13
A—Mince pie	194.1	....	.64	6
*A—Lamb stew	193.6	39.6	.65	4
*A—Broiled salt mackerel with mashed potatoes	192.2	44.1	.65	3
Cherry pie	191.5	....	.65	7
Pound cake	191.5	....	.65	7
A—Chicken cutlet and mashed potatoes.	191.2	57.6	.65	4
*A—Shredded wheat and milk	190.8	....	.66	7
Cream tapioca pudding	189.6	....	.66	13
Soda crackers and milk	188.6	....	.66	7
Strawberry pie	188.0	....	.66	7
Chocolate éclair	188.0	....	.67	13
*A—Baked lamb pie (individual)	187.7	46.6	.67	4
*A—Corned beef sandwich	186.0	79.1	.67	13
A—Broiled bacon	185.3	34.3	.67	3

Name of Food.	Nutritional Calories for Five Cents.	Per Cent. in Bread and Butter.	Cost of 2500 Calories.	No. of Orders to Make 2500 Calories.
Rice cakes with maple cane syrup	185.6	....	$0.67	4
A—Cold ham	183.5	39.6	.68	5
A—Roast beef croquettes and spaghetti	183.0	....	.68	5
*A—Chipped beef and scrambled egg	182.7	36.4	.68	3
A—Minced ham with scrambled eggs	181.9	35.5	.69	3
Peach pie	181.8	....	.69	7
A—Baked macaroni and cheese	181.6	40.5	.69	7
Huckleberry pie	179.7	....	.70	7
French toast with maple cane syrup	179.2	....	.70	4
*A—Corned beef and New York beans	179.1	....	.70	5
Blackberry pie	177.9	....	.70	7
*A—Veal pot-pie with dumplings	174.9	47.9	.71	5
*A—Creamed codfish on toast	174.7	46.3	.72	5
A—Vienna roast with stewed tomatoes	174.7	31.3	.72	5
*A—Tomato omelet	174.4	55.3	.72	4
A—Small oyster fry	174.2	36.6	.72	4
Hot rice with cream	173.3	....	.72	5
A—Plain oyster fry with bacon	171.8	32.0	.73	4
*A—Hamburger steak	170.5	29.9	.73	4
A—Corned beef hash, browned in pan	170.3	46.1	.73	5
A—Corned beef hash, steamed	169.3	55.8	.74	5
Cream	168.7	....	.74	5
*A—Chicken wings on toast	168.2	38.2	.74	4
A—Country sausage and French fried potatoes	167.2	....	.75	5
*A—Corned beef and Boston beans	166.7	48.6	.75	5
*A—Two fried eggs	166.0	58.1	.75	5
*A—Ham omelet	165.6	35.5	.75	4
*A—Plain omelet	165.5	47.2	.75	5
*A—Fried liver and mashed potatoes	164.8	51.7	.76	5
*A—Creamed chipped beef	163.7	51.7	.76	5
A—Large oyster fry	161.8	35.1	.77	3
Apple fritters with fruit sauce	161.7	....	.77	8
A—Fish cakes with tomato sauce	161.2	54.4	.78	5
French fried potatoes, extra order	160.4	....	.78	8
Chocolate cornstarch with whipped cream	159.6	....	.78	16
Shredded wheat and cream	159.5	....	.78	6
A—Chicken croquette and French fried potatoes	159.3	....	.78	5
*A—Corned beef hash with poached egg	158.9	35.5	.79	4
*A—Ham and eggs	158.3	29.8	.79	3
A—Ham and potato salad	158.1	31.1	.79	4
*A—Baked shad and dressing	157.7	....	.79	4
*A—Hamburger steak with Spanish sauce	157.4	33.7	.79	4
Charlotte russe	156.5	....	.80	16
*A—Creamed eggs on toast	155.6	37.6	.80	4
A—Bacon and eggs	155.3	29.8	.81	3
Strawberry fruit jelly with whipped cream	154.9	....	.81	16

Name of Food.	Nutritional Calories for Five Cents.	Per Cent. in Bread and Butter.	Cost of 2500 Calories.	No. of Orders to Make 2500 Calories.
*A—Buckwheat cakes with country sausage	154.7	....	$0.81	4
A—Oyster sandwich	153.8	46.3	.81	8
*A—Chicken giblets on toast	153.0	41.5	.82	4
Hot rice with butter	152.6	....	.82	8
Pimento olive cheese sandwich	152.3	87.0	.82	16
*A—Liver and bacon with lyonnaise potatoes	151.0	29.7	.83	3
*A—Corned beef hash, browned, with two poached eggs	150.1	37.7	.83	3
Buttered toast	149.7	....	.83	8
*A—Liver and bacon	149.4	36.4	.84	3
*A—Chicken hash	146.9	46.3	.85	6
A—Two scrambled eggs	146.3	52.6	.85	6
*A—Milk	145.3	....	.86	9
Apple sauce with whipped cream	144.2	....	.87	17
Hot rice with poached egg	143.3	49.8	.87	6
*A—Corned beef with potato salad	143.1	53.1	.87	6
Fish cakes with poached egg	141.8	53.2	.88	4
*A—Cold roast beef	140.1	63.4	.89	6
A—Hot rice with milk	139.6	....	.90	9
*A—Small steak	138.0	28.3	.91	3
Baked apple	136.8	....	.91	18
Baked apple with ice cream	136.0	....	.92	9
A—Two lamb chops	135.3	....	.92	3
A—Chicken salad sandwich	134.7	....	.93	9
*A—Corned beef hash, steamed, with poached egg	133.8	44.3	.93	5
* —Boston beans, on side	133.7	....	.94	19
Tomato sandwich	133.6	96.5	.94	19
A—Lamb chops, breaded, with mashed potatoes	132.7	48.6	.94	5
*A—Maple flakes with milk	132.6	....	.94	9
*A—Corned beef	132.4	45.8	.94	6
*A—Bulgarzoon	132.1	....	.95	19
A—Spanish omelet with French fried potatoes	132.1	39.8	.95	4
Baked apple custard with whipped cream	131.5	....	.95	10
Boiled rice, side order	130.8	....	.96	19
*A—Fried egg sandwich	129.6	64.7	.96	10
*A—Onion omelet	129.1	27.0	.97	5
*A—Baked weak fish with dressing	128.9	45.0	.97	5
*A—Sirloin steak	128.1	20.1	.98	2
Fresh cooked oatmeal with cream	127.7	....	.98	6
*A—Fish cakes with macaroni	126.9	....	.99	5
Sliced bananas with cream	126.2	....	.99	10
* —Macaroni, side order	125.8	....	.99	20
*A—Roast sirloin of beef and mashed potatoes	124.9	44.8	1.00	5

Name of Food.	Nutritional Calories for Five Cents.	Per Cent. in Bread and Butter.	Cost of 2500 Calories.	No. of Orders to Make 2500 Calories.
A—Tomato omelet with potatoes	121.9	42.9	$1.03	4
*A—Two boiled eggs	121.6	....	1.03	7
*A—Fish cakes with spaghetti	120.6	54.0	1.04	5
*A—Macaroni omelet with tomato sauce	119.1	38.5	1.05	4
*A—Small steak with onions	118.3	25.8	1.06	3
*A—Fish cake sandwich	117.8	....	1.06	11
*A—Egg salad	116.0	54.9	1.08	5
*A—Parsley omelet	115.2	53.1	1.09	5
Green split pea soup	114.1	59.4	1.10	11
Vanilla ice cream	113.8	....	1.10	11
*A—Tenderloin steak with onions	113.3	24.5	1.10	2
*A—Cornflakes and milk	111.1	....	1.12	11
Strawberry tart	111.0	....	1.13	11
*A—Tuna fish salad	110.9	43.0	1.13	5
*A—Sirloin steak with onions	110.0	20.1	1.14	2
Pineapple fruit jelly with whipped cream	109.8	....	1.14	23
*A—Cup custard	109.5	....	1.14	11
*A—Roast beef with potato salad	107.4	43.9	1.16	5
*A—Tenderloin steak	106.3	19.8	1.18	2
A—Milk toast	105.6	....	1.18	8
Strawberry cornstarch with whipped cream	102.2	....	1.22	24
Strawberry ice cream	102.1	....	1.22	12
*A—Clam chowder	100.6	....	1.24	6
* —Chicken soup	100.4	49.5	1.24	8
*A—Crab meat salad	99.5	68.1	1.26	6
Vegetable soup	98.1	79.6	1.27	13
Stewed rhubarb	93.9	....	1.33	27
*A—Creamed chicken on toast	92.9	37.5	1.35	7
Strawberries with cream	91.9	....	1.36	9
Strawberry short cake	91.8	....	1.36	9
*A—Chicken omelet	90.8	32.1	1.38	6
*A—Deviled crab	90.7	64.1	1.38	7
Sliced bananas	89.9	....	1.39	28
*A—Spaghetti and cheese	88.0	....	1.42	14
*A—Fried ham	86.8	49.6	1.44	6
A—Minced chicken sandwich with lettuce	86.3	....	1.45	15
* —Bean soup with croutons	84.4	....	1.48	15
*A—Hot roast beef sandwich	81.5	....	1.53	10
*A—Club sandwich	81.4	....	1.54	6
*A—Sliced chicken sandwich	78.1	....	1.60	16
*A—Poached eggs on toast	65.6	....	1.91	10
Strawberries with ice cream	65.0	....	1.92	13
* —Cream of wheat	63.0	....	1.98	20
Blackberries and cream	56.5	....	2.21	22
Stewed corn	52.5	....	2.38	48
* —Creamed asparagus on toast	49.2	....	2.54	13
Watermelon	39.4	....	3.17	20

Name of Food.	Nutritional Calories for Five Cents.	Per Cent. in Bread and Butter.	Cost of 2500 Calories.	No. of Orders to Make 2500 Calories.
* —Tomato soup with rice	36.6	....	$3.42	34
Sliced pineapple	35.3	....	3.54	71
Grape fruit	25.8	....	4.85	32
*A—Raw oysters	18.6	....	6.72	45
Sliced tomatoes with lettuce	16.6	....	7.53	50
* —Sliced tomatoes	15.2	....	8.20	82
Tomatoes with lettuce dressing	13.5	....	9.26	47
Cantaloupe	12.1	....	10.33	69
Champagne†	8.6	....	14.53	7

† Not purchased in the restaurant.

The main objection that has been encountered to the sale of food on the caloric basis has been the sensitiveness of the business world to the introduction of a new and unknown quantity. Why not leave well enough alone?

A more highly educated generation will, however, demand that its expenditure of thousands of millions of dollars for food shall not continue to take place in unfathomable depths of darkness.

For the purpose of dealing with the unintelligent masses in actual need of food the writer recommended to Dr. Haven Emerson, the local Commissioner of Health in New York City, that grocers be persuaded to prepare "Board of Health baskets" to provide 10,000 calories daily for a family of 5 at a minimum cost. The occasion was that of a general strike in the cloak-making trade. The baskets were reminiscent of the poorhouse fare in Finland (see p. 351) and should be understood as representing minima for a family out of work. Basket I is not to be commended for constant use over a prolonged period, though Basket II would probably suffice for maintenance and growth during many months.

HEALTH BASKETS

(Low cost meatless dietary for a family of 5—two adults and three children over five years—designed to maintain efficiency for one day, June, 1916)

Articles Arranged in the Order of Increasing Cost of Fuel Value.	Basket I. Possible Minimum.			Basket II. Desirable Minimum.		
	Pounds.	Calories.	Cost.	Pounds.	Calories.	Cost.
Cornmeal	1					
Hominy	1	1750	.03	1	1750	.03
Oatmeal	1					
Sugar	1	1800	.08	1	1800	.08
Rice						
Bread	2¼*	2800	.09	2¼	2800	.09
Corn syrup or molasses.	⅓	500	.02	⅓	500	.02
Pork (fat)						
Beans (dried)						
Oleomargarin	½	1800	.11½	½	1800	.11½
Potatoes	..	....	...	3½	1000	.10
Milk	4†	1270	.12	4	1270	.12
Apples	..	....	...	2	500	.10
		9920	.45½		11,420	.65½

* Three loaves of 12-ounce day-old bread, 3 cents a loaf. Rice, 1½ pounds (2625 calories) costs 7½ cents and may in part be used instead of bread.

† Two quarts of milk at 6 cents a quart.

Notes on preparation of food:

Oatmeal contains valuable iron and calcium salts. Boil one-half hour.

Hominy.—Soak in water over night. Boil one and one-half hours.

Cornmeal.—Boil one-half hour.

Rice.—Twenty-five minutes' rapid boiling.

Potatoes.—Boil one-half to three-quarters of an hour.

Beans.—High in protein and calcium. Soak over night and boil two to two and one-half hours.

Rubner[1] has set forth his ideas of true reform with regard to the question of the nourishment of the masses. There should be less profit to middlemen. If food must be eaten outside the home, there should be cheap restaurants or public kitchens where nourishing food can be purchased. It is cheaper to cook in one's own kitchen provided the fire that is used for cooking is needed for heating. The personal ownership of a house and garden to the wide-spread extent of such ownership in America must be morally uplifting for a community. For this reason factories should be built in the

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[1] Rubner: "Wandlungen in der Volksernährung," Leipzig, 1913.

country. Furthermore, children are more useful in the country than in the city. The cost of rooms in which to live bears an intimate relation to the amount of money available for food. Not only are quarters costly in the town, but many landlords classify children with cats and dogs as undesirable tenants.

The housewife should know about cooking, and both she and her husband should know something of the value of food. The sum wasted for alcoholic beverages would frequently be sufficient to turn the scale in favor of the proper nutrition of the family. Cheaper milk for the babies of the poor and adequate nourishment for school children are important factors in the situation. Rubner regrets that the knowledge of biology, even among the educated classes, is so limited that the science of nutrition appears to them to be wholly useless.

Rubner's words were written in contemplation of a highly developed modern community and before the outbreak of the war. The story of the regulation and conservation of the food supply by the state under scientific direction is yet to be written. An enforced abstinence from alcohol cannot possibly be harmful, but whether the introduction each week of two or three "meatless days" into the regimen of adults, and especially of children, is for their permanent welfare cannot at present be determined. The psychologic factor alone is of too profound significance to give credence to the value of any personal opinion.

As this book goes to press it seems that America herself is certain to face a food shortage before very long. This can be remedied by increasing the number of milch cows and by reducing the livestock raised for meat. The latter would free arable land for the production of grain and potatoes and save, for human consumption, grain fed to steers. It is quite certain that meat in the quantity it is consumed today is entirely unnecessary, and it is susceptible of scientific proof (see p. 312) that mechanical work is more efficiently and economically derived from carbohydrate food than from meat.

APPENDIX

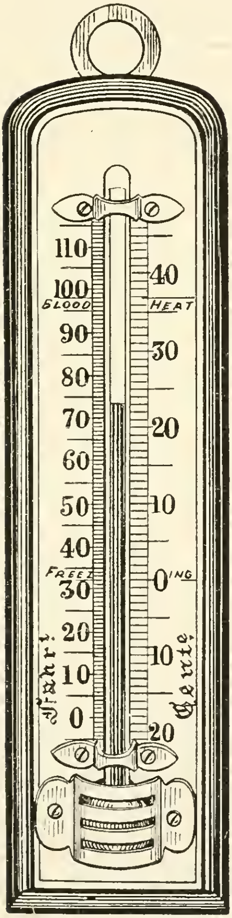

Fig. 28.—Thermometer showing comparison of Fahrenheit and Centigrade scales.

CONVENIENT COMPARISONS OF METRIC AND AVOIRDUPOIS WEIGHTS

1 kilogram = 2.2046 pounds
1 pound = 453.6 grams
1 ounce = 28.3 grams
1 liter = 61.027 cubic inches = 1.7608 pints
1 gram-calorie = 0.425 kilogram-meters of mechanical energy
1 meter = 3.2809 feet
1 kilometer = 0.6214 miles

THE CHEMICAL COMPOSITION OF NORMAL URINES ON PURIN-FREE DIETS. (After Folin, see p. 209.)

	Person.						
	E. S. A.		H. B. H.				
	June.		March.			July.	
	29th	30th	8th	9th	10th	13th	20th
Total N in grams	14.6	15.8	15.9	15.5	15.0	16.8	3.6
Urea N	12.6	13.9	13.5	13.4	12.9	14.7	2.2
Ammonia N	0.54	0.54	0.41	0.41	0.43	0.49	0.42
Creatinin N	0.39	0.43	0.70	0.64	0.69	0.58	0.60
Uric Acid N	0.15	0.11	0.26	0.23	0.27	0.18	0.09
Undetermined N	0.96	0.88	1.06	0.79	0.68	0.85	0.27
Total SO_3 in grams	3.02	2.94	3.03	2.49	2.19	3.64	0.76
Inorganic SO_3	2.56	2.58	2.48	2.05	1.74	3.27	0.46
Ethereal SO_3	0.26	0.22	0.20	0.18	0.19	0.19	0.10
Neutral SO_3	0.20	0.14	0.35	0.26	0.26	0.18	0.20
In per cent. of total N:							
Urea N	86.0	87.7	84.7	86.4	86.2	87.5	61.7
Ammonia N	3.6	3.3	2.6	2.7	2.9	3.0	11.3
Creatinin N	2.7	2.7	4.4	4.1	4.6	3.6	17.2
Uric Acid N	1.0	0.7	1.6	1.7	1.8	1.05	2.5
Undetermined N	6.6	5.6	6.7	5.1	4.4	4.85	7.3
In per cent. of total SO_3:							
Inorganic SO_3	84.7	87.7	81.8	82.0	79.4	90.0	60.5
Ethereal SO_3	8.6	7.4	6.6	7.2	8.6	5.2	13.2
Neutral SO_3	6.7	4.9	11.6	10.8	12.0	4.8	26.5

YEAR OF 1905

TABLE SHOWING THE COST OF PROTEIN AND ENERGY

As Furnished by a Number of Common Food Materials, at Prices Current in the Eastern Part of the United States

Compiled by Langworthy, U. S. Department of Agriculture, 1905, in Farmers' Bulletin, No. 85, p. 19.

Note that the prices for 1917 are double or triple those given here. Compare with prices of 1915 on p. 561.

(1 pound = 453.6 grams.)

Kind of Food Material.	Price per Pound.	Cost of 1 Pound Protein.	Cost of 1000 Calories Energy.	Amounts for 10 Cents.		
				Total Weight of Food Material.	Protein.	Energy.
	Cents.	*Dollars.*	*Cents.*	*Lbs.*	*Lb.*	*Calories.*
Codfish, whole, fresh	10	0.90	48	1.000	0.111	209
Codfish, steaks	12	.71	36	.833	.142	274
Bluefish	12	1.20	58	.833	.083	172
Halibut	18	1.18	40	.556	.085	253
Codfish, salt	7	.44	23	1.429	.229	437
Mackerel, salt	10	.61	10	1.000	.163	998
Salmon, canned	12	.62	18	.833	.162	547
Oysters (solids, 30 cents quart)	15	2.50	68	.667	.040	147
Oysters (solids, 60 cents quart)	30	5.00	136	.333	.020	74
Lobster	18	3.05	129	.556	.033	77
Beef, sirloin steak	25	1.52	26	.400	.066	380
Beef, sirloin steak	20	1.21	21	.500	.083	475
Beef, round	14	.74	16	.714	.136	615
Beef, stew meat	5	.38	5	2.000	.266	1862
Beef, dried, chipped	25	.95	33	.400	.106	303
Mutton chops, loin	20	1.48	14	.500	.068	694
Mutton, leg	22	1.46	25	.454	.069	394
Pork, roast, loin	12	.90	10	.833	.112	1016
Pork, smoked ham	22	1.55	14	.454	.064	729
Milk (7 cents quart)	3	1.06	11	2.857	.094	891
Milk (6 cents quart)	3	.91	10	3.333	.110	1040
Wheat flour	3	.26	2	3.333	.380	5363
Corn meal	2	.22	1	5.000	.460	8055
Potatoes (90 cents bushel)	1½	.83	5	6.667	.120	2020
Potatoes (45 cents bushel)	¾	.42	2	13.333	.240	4040
Cabbage	2½	1.79	21	4.000	.056	484
Corn, canned	10	3.57	23	1.000	.028	444
Apples	1½	5.00	7	6.667	.020	1420
Bananas	7	8.75	24	1.429	.011	414
Strawberries	7	7.78	42	1.429	.013	240

A more extensive compilation, which permits not only the calculation of the nutritive value of the particular edible food but also of the approximate weight of inedible waste entailed in the direct purchase of the material in the market, is as follows:

COMPOSITION OF ORDINARY FOOD MATERIALS

According to Atwater and Bryant.

Report of the Storrs Agricultural Experiment Station, 1899, p. 113, somewhat abridged.

Kind of Food Material.	Inedible Refuse of Purchased Material.	Edible Portion.						
		Water.	Unavailable Nutrients.	Available Nutrients.				
				Protein.	Fat.	Carbohydrates.	Ash.	Fuel value per lb. =453.6 Grams.
Animal Foods.								
Beef (fresh).	%	%	%	%	%	%	%	Calories.
Brisket	23.3	54.6	2.1	15.3	27.1	...	.7	1475
Chuck	16.3	62.7	1.8	17.9	17.1	...	.7	1095
Flank	10.2	60.2	1.9	18.3	19.9	...	.7	1225
Loin, lean	13.1	67.0	1.2	19.1	12.1	...	1.0	900
Loin, medium	13.3	60.6	1.8	17.9	19.2	...	.8	1185
Loin, fat	10.2	54.7	1.9	17.0	26.2	...	.9	1470
Neck	27.6	63.4	1.6	19.5	15.7	...	.7	1065
Plate	16.5	54.4	2.2	16.0	27.6	...	.6	1510
Ribs	20.8	55.5	2.0	17.0	25.3	...	.7	1430
Round, lean	8.1	70.0	1.0	20.7	7.5	...	1.1	735
Round, medium	7.2	65.5	1.6	10.7	12.9	...	.8	950
Round, fat	12.0	60.4	1.6	18.9	18.5	...	1.0	1175
Round, second cut	19.5	69.8	1.3	19.8	8.2	...	.8	750
Rump	20.7	56.7	2.0	16.9	24.2	...	.7	1380
Fore shank	36.9	67.9	1.4	19.8	11.0	...	.7	865
Tongue	26.5	70.8	1.3	18.3	8.7	...	.8	740
Shoulder and clod	16.4	68.3	1.5	19.0	10.7	...	.8	840
Fore quarter	18.7	60.4	1.8	17.4	20.3	...	.7	1220
Hind quarter	15.7	59.8	1.8	17.8	20.5	...	.7	1240
Side, lean	19.5	67.2	1.3	18.7	12.5	...	.9	910
Side, medium	17.4	59.7	1.8	17.6	20.0	...	.7	1250
Side, fat	13.2	47.8	2.5	15.7	34.6	...	.5	1805
Liver	7.0	71.2	1.2	20.4	4.3	1.7	1.2	620
Suet (unrendered tallow)	...	13.7	4.3	4.6	77.7	...	.2	3440
Hind shank	53.9	67.8	1.4	20.3	10.9	...	.7	875
Beef (preserved and cooked).								
Dried and smoked	4.7	54.3	3.5	29.1	6.2	...	6.8	850
Brisket, corned	21.4	50.9	3.2	17.8	23.5	...	4.2	1370
Flank, corned	12.1	49.9	2.7	14.2	31.4	...	2.2	1635

COMPOSITION OF ORDINARY FOOD MATERIALS (Continued)

Kind of Food Material.	Inedible Refuse of Purchased Material.	Edible Portion.						
		Water.	Unavailable Nutrients.	Available Nutrients.				
				Protein.	Fat.	Carbohydrates.	Ash.	Fuel value per lb. =453.6 Grams.
Animal Foods. *Beef (preserved and cooked).*	%	%	%	%	%	%	%	Calories.
Plate, corned	14.5	40.1	3.7	13.3	39.8	...	3.5	1980
Rump, corned	6.0	58.1	2.2	14.8	22.1	...	2.8	1250
Canned, boiled	...	51.8	2.2	24.7	21.4	...	1.0	1415
Canned, corned	...	51.8	2.7	25.5	17.8	...	3.0	1275
Boiled beef (cut not given)	...	38.1	2.7	25.4	33.2	...	.7	1930
Roast, cooked	...	48.2	2.4	21.6	27.2	...	1.0	1410
Loin steak, cooked	...	54.8	2.0	22.8	19.4	...	.9	1290
Tripe, pickled	...	86.5	.6	11.3	1.1	...	.2	275
Veal (fresh).								
Breast	21.3	66.0	1.5	18.9	13.3	...	.8	950
Chuck	18.9	73.0	1.1	19.1	6.2	...	.8	650
Cutlets (round)	3.4	70.7	1.3	19.7	7.3	...	.8	710
Flank	...	68.9	1.3	19.9	9.0	...	.8	825
Leg	14.2	70.0	1.3	19.6	8.6	...	.9	760
Loin	16.5	69.0	1.3	19.3	10.3	...	.8	830
Neck	31.5	72.6	1.1	19.7	6.6	...	.8	680
Rib	24.3	72.7	1.2	20.1	5.8	...	.8	650
Shank	62.7	74.5	1.0	20.1	4.4	...	.8	590
Fore quarter	24.5	71.7	1.2	19.4	7.6	...	.7	715
Hind quarter	20.7	70.9	1.2	20.1	7.9	...	.8	740
Side	22.6	71.3	1.2	19.6	7.7	...	8	725
Liver	...	73.0	.9	9.7	5.0	...	1.0	410
Lamb (fresh).								
Breast or chuck	19.1	56.2	2.0	18.5	22.4	...	.8	1335
Leg	17.4	63.9	1.7	18.6	15.7	...	.8	1050
Loin	14.8	53.1	2.2	18.1	26.9	...	.8	1520
Neck	17.7	56.7	1.9	17.2	23.6	...	.8	1360
Shoulder	20.3	51.8	2.2	17.6	28.2	...	.8	1565
Fore quarter	18.8	55.1	2.0	17.8	24.5	...	.8	1410
Hind quarter	15.7	60.9	1.8	19.0	18.1	...	.8	1160
Side	19.3	58.2	2.0	17.1	21.9	...	.8	1285
Lamb (cooked).								
Chops, broiled	13.5	47.6	2.5	21.0	28.4	...	1.0	1640
Leg, roast	...	67.1	1.4	19.1	12.1	...	.6	905
Mutton (fresh).								
Chuck	21.3	50.9	2.4	14.6	31.9	...	.7	1665
Flank	9.9	46.2	2.6	14.7	36.4	...	.5	1860

COMPOSITION OF ORDINARY FOOD MATERIALS (Continued)

Kind of Food Material.	Inedible Refuse of Purchased Material.	Edible Portion.						
		Water.	Unavailable Nutrients.	Available Nutrients.				
				Protein.	Fat.	Carbohydrates.	Ash.	Fuel value per lb. =453.6 Grams.
Animal Foods.								
Mutton (fresh).	%	%	%	%	%	%	%	Calories.
Leg	18.4	62.8	1.7	17.9	17.1	...	.8	1095
Loin	16.0	50.2	2.4	1.55	31.4	...	.6	1660
Neck	27.4	58.1	2.0	16.4	23.4	...	.7	1335
Shoulder	22.5	61.9	1.7	17.2	18.9	...	.7	1160
Fore quarter	21.2	52.9	2.2	15.1	29.4	...	.7	1570
Hind quarter	17.2	54.8	2.1	16.2	26.7	...	.6	1475
Side	18.1	54.2	2.1	15.8	27.5	...	.7	1500
Mutton (cooked and canned).								
Leg, roast	...	50.9	2.1	24.3	21.5	...	.9	1410
Corned, canned	...	45.8	3.0	27.9	21.7	...	3.2	1495
Tongue, canned	...	47.6	3.1	23.7	22.8	...	3.6	1045
Pork (fresh).								
Chuck, ribs and shoulder	18.1	51.1	2.3	16.8	29.5	...	.7	1605
Flank	18.0	59.0	1.9	17.9	21.1	...	.8	1265
Loin, chops	19.7	52.0	2.2	16.1	28.6	...	.8	1555
Ham	10.7	53.9	2.1	14.8	27.5	...	.6	1480
Shoulder	12.4	51.2	2.3	12.9	32.5	...	.6	1660
Side	11.5	34.4	3.2	8.8	52.5	...	.4	2440
Pork (pickled, salted, and smoked).								
Bacon	7.7	18.8	4.8	9.6	64.0	...	3.3	2950
Ham	13.6	40.3	3.6	15.8	36.9	...	3.6	1905
Shoulder	18.2	45.0	3.8	15.4	30.9	...	5.0	1640
Salt, lean ends	11.2	19.9	5.1	8.1	63.7	...	4.3	2905
Salt, fat	...	7.9	5.4	1.8	81.9	...	2.9	3565
Pigs' feet, pickled	35.5	68.2	1.4	15.8	14.1	...	.7	920
Pork (cooked).								
Ribs, cooked	...	33.6	3.1	24.1	35.7	...	1.7	2020
Steak, cooked	...	33.2	3.3	19.3	43.1	...	1.1	2245
Sausage.								
Bologna	3.3	60.0	2.4	18.1	16.7	0.3	2.8	1085
Frankfort	...	57.2	2.3	19.0	17.7	1.1	2.6	1160
Pork	...	39.8	3.1	12.6	42.0	1.1	1.7	2080
Poultry and game (fresh).								
Chicken, broilers	41.6	74.8	1.0	20.9	2.4	...	.8	520
Fowl	25.9	63.7	1.6	18.7	15.5	...	.8	1040
Goose	17.6	46.7	2.5	15.8	34.4	...	.6	1800
Turkey	22.7	55.5	1.9	20.5	21.8	...	.8	853

COMPOSITION OF ORDINARY FOOD MATERIALS (Continued)

Kind of Food Material.	Inedible Refuse of Purchased Material.	Edible Portion.						
		Water.	Unavailable Nutrients.	Available Nutrients.				
				Protein.	Fat.	Carbohydrates.	Ash.	Fuel value per lb. =453.6 Grams.
Animal Foods.								
Poultry and game (cooked and canned).	%	%	%	%	%	%	%	Calories.
Capon	10.4	59.9	1.7	26.2	10.9	...	1.0	995
Turkey, roast	...	67.5	1.3	17.1	10.9	.8	2.4	855
Plover, roast, canned	...	57.7	1.7	21.7	9.7	1.6	7.6	985
Quail, canned	...	66.9	1.6	21.1	7.6	1.1	1.7	780
Fish (fresh).								
Bass, black, whole	54.8	76.7	1.0	20.0	1.6	...	.9	470
Bluefish	48.6	78.5	1.0	18.8	1.1	...	1.0	420
Codfish, dressed	29.9	58.5	.5	10.8	.2	...	.6	225
Cod steaks	9.2	79.7	.9	18.1	.5	...	.9	385
Flounder, whole	61.5	84.2	.7	13.8	.6	...	1.0	300
Haddock	51.0	81.7	.8	16.7	.3	...	.9	345
Halibut steak	17.7	75.4	1.1	18.0	4.9	...	.8	570
Lake trout	48.5	70.8	1.3	17.3	9.8	...	.9	765
Mackerel	44.7	73.4	1.3	18.1	6.7	...	.9	650
Weakfish	51.9	79.0	.9	17.3	2.3	...	.9	445
Whitefish, whole	53.5	69.8	1.4	22.2	6.2	...	1.2	710
Shell-fish (fresh).								
Long clams, in shell	41.9	85.8	1.0	8.3	.9	2.0	2.0	240
Round clams, in shell	67.5	86.2	.9	6.3	.4	4.2	2.0	215
Oysters, in shell	81.4	86.9	.8	6.0	1.1	3.7	1.5	235
Oysters, solids	...	88.3	.6	5.8	1.2	3.3	.8	225
Clams, round, solids	...	80.8	1.0	10.3	1.0	5.2	1.7	340
Crabs, hard shells	52.4	77.1	1.4	16.1	1.9	1.2	2.3	425
Lobster	61.7	79.2	1.1	15.9	1.7	.4	1.7	400
Fish (preserved and canned).								
Cod, salt	24.9	53.5	6.8	20.9	.3	...	18.5	430
Cod, salt, boneless	1.6	55.0	5.5	24.9	.3	...	14.3	510
Halibut, smoked	7.0	49.4	5.0	20.1	14.3	...	11.3	1015
Herring, smoked	44.4	34.6	5.2	35.8	15.0	...	9.9	1360
Mackerel, salt, dressed	19.7	43.4	5.0	16.8	25.1	...	9.7	1415
Salmon, canned	14.2	63.5	1.9	21.1	11.5	...	2.0	915
Sardines, canned	5.0	52.3	3.1	22.3	18.7	...	4.2	1250
Lobster, canned	...	77.8	1.3	17.6	1.0	.4	1.9	400
Clams, canned	...	82.9	1.0	10.2	.8	3.0	2.1	290
Oysters, canned	...	83.4	.8	8.5	2.3	3.9	1.1	340

COMPOSITION OF ORDINARY FOOD MATERIALS (Continued)

Kind of Food Material.	Inedible Refuse of Purchased Material.	Edible Portion.						
				Available Nutrients.				
		Water.	Unavailable Nutrients.	Protein.	Fat.	Carbohydrates.	Ash.	Fuel value per lb. =453.6 Grams.
Animal Foods.								
Eggs.	%	%	%	%	%	%	%	Calories.
Eggs, uncooked	11.2	73.7	1.1	13.0	10.0	...	.8	695
Eggs, boiled	11.2	73.2	1.2	12.8	11.4	...	.6	755
Dairy products, etc.								
Whole milk	...	87.0	.5	3.2	3.8	5.0	.5	310
Skimmed milk	...	90.5	.3	3.3	.3	5.1	.5	170
Condensed milk, sweetened	...	26.9	1.2	8.5	7.9	54.1	1.4	1460
Cream	...	74.0	1.1	2.4	17.6	4.5	.4	860
Cheese	...	34.2	3.4	25.1	32.0	2.4	2.9	1885
Butter	...	11.0	4.9	1.0	80.8	...	2.3	3410
Oleomargarin, etc	...	0.5	5.7	1.2	78.9	...	4.7	3335
Lard, cottolene, etc	...	...	5.0	...	95.0	...	...	3985
Animal Foods.								
Miscellaneous.								
Gelatin	...	13.6	3.2	88.7	.1	...	1.6	2125
Calf's-foot jelly	...	77.6	.3	4.2	...	17.4	.5	410
Vegetable Foods.								
Cereals, etc.								
Barley, pearled	...	11.5	4.0	6.6	1.0	76.1	.8	1630
Buckwheat flour	...	13.6	3.5	5.2	1.1	75.9	.7	1600
Buckwheat, self-raising	...	11.6	4.9	6.7	1.1	71.5	4.2	1545
Corn (maize) flour	...	12.6	3.6	5.8	1.2	76.3	.5	1625
Corn (maize) meal	...	12.5	4.0	7.5	1.7	73.5	.8	1625
Corn (maize) preparations:								
Cerealine	...	10.3	4.2	7.8	1.0	76.3	.4	1655
Hominy	...	11.8	3.8	6.8	.5	76.9	.2	1625
Hominy, cooked	...	79.3	.9	1.8	.2	17.4	.4	375
Oatmeal and rolled oats	...	7.8	5.6	13.4	6.6	65.2	1.4	1795
Oatmeal, boiled	...	84.5	.9	2.3	.5	11.3	.5	285
Rice	...	12.3	3.7	6.5	.3	76.9	.3	1610
Rice, boiled	...	72.5	1.1	2.3	.1	23.8	.2	505
Rye flour	...	12.9	3.6	5.3	.8	76.9	.5	1610
Entire wheat flour	...	11.4	4.5	10.7	1.7	70.9	.8	1645
Gluten flour	...	12.0	4.6	11.0	1.6	70.1	.7	1630
Graham flour	...	11.3	4.7	10.3	2.0	70.4	1.3	1640
Wheat flour, patent process:								
Low grade	...	12.0	4.5	10.9	1.7	70.2	.7	1635
Bakers' grade	...	11.9	4.2	10.3	1.4	7.7	.5	1640

COMPOSITION OF ORDINARY FOOD MATERIALS (Continued)

KIND OF FOOD MATERIAL.	Inedible Refuse of Purchased Material.	EDIBLE PORTION.						
				AVAILABLE NUTRIENTS.				
		Water.	Unavailable Nutrients.	Protein.	Fat.	Carbohydrates.	Ash.	Fuel value per lb. =453.6 Grams.
VEGETABLE FOODS.								
Cereals, etc.	%	%	%	%	%	%	%	Calories.
Wheat flour:								
Family and straight grade	...	12.8	4.0	8.3	1.0	73.5	.4	1615
High grade	...	12.4	4.0	8.7	.9	73.6	.4	1620
Wheat preparations:								
Breakfast foods	...	9.6	4.5	9.3	1.6	74.0	1.0	1670
Macaroni	...	10.3	4.5	10.4	.8	73.0	1.0	1640
Macaroni, cooked	...	78.4	1.3	2.3	1.4	15.6	1.0	405
Spaghetti	...	10.6	4.0	9.4	.4	75.1	.5	1640
Noodles	...	10.7	4.2	9.1	.9	74.3	.8	1640
Bread:								
Brown	...	43.6	2.8	4.2	1.6	46.2	1.6	1035
Corn (johnnycake)	...	38.9	3.5	6.5	4.2	45.2	1.7	1170
Rye	...	35.7	3.4	7.3	.5	52.0	1.1	1160
Graham	...	35.7	3.4	6.9	1.6	51.3	1.1	1185
Whole wheat	...	38.4	3.2	7.5	.8	49.1	1.0	1125
White wheat	...	35.3	3.3	7.1	1.2	52.3	.8	1195
Biscuit, soda*	...	22.9	4.7	7.2	12.3	51.8	1.1	1655
Rolls	...	29.2	3.6	6.9	3.7	55.8	.8	1360
Toasted bread	...	24.0	4.1	8.9	1.4	60.3	1.3	1390
Crackers:								
Boston (split)	...	7.5	5.0	8.5	7.7	69.9	1.4	1830
Milk, cream	...	6.8	5.0	7.5	10.9	68.5	1.3	1920
Graham	...	5.4	4.8	7.7	8.5	72.5	1.1	1900
Oyster	...	4.8	5.4	8.8	9.5	69.3	2.2	1905
Soda	...	5.9	4.9	7.6	8.2	71.8	1.6	1870
Water	...	6.8	5.0	8.3	7.9	70.6	1.4	1850
Cakes, cookies, etc.:								
Bakers' cake	...	31.4	3.3	4.8	4.1	55.8	.6	1335
Coffee cake	...	21.3	3.8	5.5	6.8	61.9	.7	1580
Gingerbread	...	18.8	4.3	4.5	8.1	62.1	2.2	1620
Sponge cake	...	15.3	4.4	4.8	9.6	64.5	1.4	1735
Drop cake	...	16.6	4.5	5.9	13.2	59.2	.6	1805
Molasses cookies	...	6.2	4.7	5.6	7.8	74.0	1.7	1855
Sugar cookies	...	8.3	4.5	5.4	9.2	71.6	1.0	1865
Ginger snaps	...	6.3	4.7	5.0	7.7	74.3	2.0	1845
Wafers	...	6.6	4.8	6.7	7.7	73.0	1.2	1855
Doughnuts	...	18.3	4.8	5.2	18.9	52.1	.7	1895
Pie, pudding, etc.:								
Pie, apple	...	42.5	3.1	2.4	8.8	41.8	1.4	1215
Pie, custard	...	62.4	2.2	3.2	5.7	25.7	.8	795
Pie, squash	...	64.2	2.4	3.4	7.6	21.4	1.0	800

* Made from wheat flour, raised with baking powder.

COMPOSITION OF ORDINARY FOOD MATERIALS (Continued)

Kind of Food Material.	Inedible Refuse of Purchased Material.	Edible Portion.						
		Water.	Unavailable Nutrients.	Available Nutrients.				
				Protein.	Fat.	Carbohydrates.	Ash.	Fuel value per lb. =453.6 Grams.
VEGETABLE FOODS.								Calories.
Cereals, etc.								
Pie, pudding, etc.:	%	%	%	%	%	%	%	
Pudding, Indian meal.	...	60.7	2.5	4.5	4.3	26.9	1.1	785
Pudding, rice custard.	...	59.4	2.1	3.2	4.1	30.7	.5	825
Pudding, tapioca	...	64.5	1.0	2.8	2.9	28.2	.6	715
Sugars, starches, etc.								
Sugar, granulated	...	...	...	...	...	100.0	...	1790
Sugar, pulverized	...	...	...	...	...	100.0	...	1790
Sugar, brown	...	...	...	...	...	95.0	...	1700
Sugar, maple	...	...	...	...	...	82.8	...	1485
Molasses	...	...	...	...	...	70.0	...	1255
Maple syrup	...	...	...	...	...	71.0	...	1270
Cornstarch	...	...	...	...	...	90.0	...	1715
Tapioca	...	11.4	.1	.3	.1	88.0	.1	1685
Sago	...	12.2	1.4	7.7	.4	78.1	.2	1665
Vegetables.								
Asparagus, fresh	...	94.0	.7	1.3	.2	3.3	.5	95
Asparagus, cooked	...	91.6	1.0	1.7	3.0	2.1	.6	195
Beans, Lima, green	55.0	68.5	2.7	5.3	.6	21.6	1.3	525
Beans, Lima, dried	...	10.4	6.7	12.8	1.4	65.6	3.1	1565
Beans, string, fresh	7.0	89.2	1.0	1.7	.3	7.2	.6	180
Beans, string, cooked*	...	95.3	.5	.6	1.0	1.9	.7	90
Beans, white, dried	...	12.6	7.5	15.8	1.6	59.9	2.6	1530
Beans, baked	...	68.9	2.8	4.8	2.3	19.6	1.6	565
Beets, fresh	20.0	87.5	1.0	1.2	.1	9.4	.8	205
Beets, cooked*	...	88.6	1.2	1.7	.1	7.2	1.2	170
Beet "greens," cooked*	...	89.5	1.2	1.7	3.1	3.2	1.3	220
Cabbage	15.0	91.5	.7	1.2	.3	5.5	.8	140
Carrots, fresh	20.0	88.2	1.0	.7	.4	8.9	.8	200
Carrots, evaporated	...	3.5	6.9	5.8	3.2	76.9	3.7	1700
Cauliflower	...	92.3	.7	1.3	.5	4.7	.5	135
Celery	20.0	94.5	.6	.8	.1	3.2	.8	80
Sweet corn, green	61.0	75.4	1.8	2.3	1.0	19.0	.5	445
Cucumbers	15.0	95.4	.4	.6	.2	3.0	.4	75
Egg plant	...	92.9	.6	.9	.3	4.9	.4	120
Lettuce	15.0	94.7	.5	.9	.3	2.9	.7	85
Onions, fresh	10.0	87.6	.8	1.2	.3	9.6	.5	215
Onions, cooked*	...	91.2	.8	.9	1.6	4.8	.7	175
Parsnips	20.0	83.0	1.2	1.2	.5	13.0	1.1	290
Peas, dried	...	9.5	7.6	17.3	.9	62.5	2.2	1508
Peas, green	45.0	74.6	2.2	5.2	.5	16.7	.8	430

* With butter, etc., added.

COMPOSITION OF ORDINARY FOOD MATERIALS (Continued)

Kind of Food Material.	Inedible Refuse of Purchased Material.	Edible Portion.						
				Available Nutrients.				
		Water.	Unavailable Nutrients.	Protein.	Fat.	Carbohydrates.	Ash.	Fuel value per lb. =453.6 Grams.
Vegetable Foods.								
Vegetables.	%	%	%	%	%	%	%	Calories.
Peas, green, cooked*	...	73.8	2.5	5.1	3.1	14.4	1.1	490
Potatoes	20.0	78.3	1.4	1.7	.1	17.7	.8	370
Potatoes, cooked, boiled	...	75.5	1.7	1.9	.1	20.0	.8	415
Potatoes, mashed and creamed	...	75.1	2.0	2.0	2.7	17.1	1.1	475
Pumpkins	50.0	93.1	.6	.7	.1	5.0	.5	110
Radishes	30.0	91.8	.7	1.0	.1	5.6	.8	130
Rhubarb	40.0	94.4	.6	.4	.6	3.5	.5	100
Squash	50.0	88.3	.9	1.1	.5	8.6	.6	205
Spinach, fresh	...	92.3	1.0	1.6	.3	3.2	1.6	100
Spinach, cooked*	...	89.8	1.1	1.6	3.7	2.7	1.1	235
Sweet potatoes, fresh	20.0	69.0	2.1	1.3	.6	26.2	.8	545
Sweet potatoes, cooked*	...	51.9	3.0	2.2	1.9	40.3	.7	885
Tomatoes	...	94.3	.4	.7	.4	3.8	.4	100
Turnips	30.0	89.6	.8	1.0	.2	7.8	.6	175
Vegetables (canned).								
Asparagus	...	94.4	.6	1.2	.1	2.8	.9	80
Beans, baked	...	68.9	2.7	4.8	2.3	19.7	1.6	555
Beans, string	...	93.7	.7	.8	.1	3.7	1.0	90
Beans, Lima	...	79.5	1.7	3.0	.3	14.3	1.2	335
Sweet corn	...	76.1	1.7	2.1	1.1	18.3	.7	430
Peas, green	...	85.3	1.4	2.7	.2	9.6	.8	235
Succotash	...	75.9	1.8	2.7	.9	18.0	.7	425
Tomatoes	...	94.0	.5	.9	.2	3.9	.5	100
Fruits, etc. (fresh).								
Apples	25.0	84.6	1.6	.3	.5	12.8	.2	260
Apricots	6.0	85.0	1.5	.9	...	12.2	.4	240
Bananas	35.0	75.3	2.7	1.0	.5	19.9	.6	400
Blackberries	...	86.3	1.5	1.0	.9	9.9	.4	235
Cherries	5.0	80.9	2.0	.8	.7	15.1	.5	320
Cranberries	...	88.9	1.2	.3	.5	8.9	.2	190
Currants	...	85.0	1.7	1.2	...	11.6	.5	230
Figs	...	79.1	2.2	1.2	...	17.0	.5	330
Grapes	25.0	77.4	2.4	1.1	1.4	17.3	.4	390
Huckleberries	...	81.9	2.0	.5	.5	14.9	.2	300
Lemons	30.0	89.3	1.2	.8	.6	7.7	.4	180
Muskmelons	50.0	89.5	1.1	.5	...	8.4	.5	160
Oranges	27.0	86.9	1.4	.6	.2	10.5	.4	210
Pears	10.0	84.4	1.7	.5	.4	12.7	.3	255
Plums	5.0	78.4	2.2	.8	...	18.2	.4	345

* With butter, etc., added.

COMPOSITION OF ORDINARY FOOD MATERIALS (Continued)

Kind of Food Material.	Inedible Refuse of Purchased Material.	Edible Portion.						
		Water.	Unavailable Nutrients.	Available Nutrients.				
				Protein.	Fat.	Carbohydrates.	Ash.	Fuel value per lb. =453.6 Grams.
Vegetable Foods.								
Fruits, etc. (fresh).	%	%	%	%	%	%	%	Calories.
Prunes	6.0	79.6	2.1	.7	...	17.1	.5	325
Raspberries, black	...	84.1	1.7	1.4	.9	11.4	.5	270
Strawberries	5.0	90.4	1.0	.8	.5	6.8	.5	160
Watermelons	60.0	92.4	.9	.3	.2	6.0	.2	125
Fruits, etc. (dried).								
Apples	...	28.1	7.5	1.3	2.0	59.6	1.5	1190
Apricots	...	29.4	7.7	3.7	.9	56.5	1.8	1130
Citron	...	19.0	8.3	.4	1.3	70.3	.7	1340
Currants	...	17.2	8.6	1.9	1.5	67.0	3.8	1315
Dates	10.0	15.4	8.8	1.6	2.5	70.7	1.0	1415
Figs	...	18.8	8.7	3.4	.3	67.0	1.8	1290
Raisins	10.0	14.6	9.1	2.0	3.0	68.7	2.6	1410
Prunes	15.0	22.3	8.3	1.6	...	66.1	1.7	1230
Fruits, etc. (canned).								
Apricots	...	81.4	1.9	.7	...	15.7	.3	295
Blackberries	...	40.0	6.1	.6	1.9	50.9	.5	1015
Blueberries	...	85.6	1.6	.5	.5	11.5	.3	240
Cherries	...	77.2	2.3	.9	.1	19.1	.4	365
Crab-apples	...	42.4	5.7	.3	2.2	49.0	.4	985
Peaches	...	88.1	1.3	.5	.1	9.8	.2	190
Pears	...	81.1	1.9	.3	.3	16.2	.2	310
Strawberries (stewed)	...	74.8	2.6	.5	...	21.7	.4	400
Nuts.								
Almonds	45.0	4.8	10.9	17.8	49.4	15.6	1.5	2685
Butternuts	86.0	4.4	11.4	23.7	55.1	3.2	2.2	2805
Chestnuts (fresh)	16.0	45.0	5.9	5.3	4.9	37.9	1.0	990
Cocoanuts	49.0	14.1	9.2	4.8	45.5	25.1	1.3	2460
Filberts	52.0	3.7	10.7	13.3	58.8	11.7	1.8	2930
Hickorynuts	62.0	3.7	10.6	13.1	60.7	10.3	1.6	2980
Peanuts	25.0	9.2	10.7	21.9	34.7	22.0	1.5	2255

For greater detail see The Chemical Composition of American Food Materials, by Atwater and Bryant, Bulletin 28 (Revised), U. S. Dept. of Agriculture, Washington, 1902.

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